March, 1961
volume 81, number 3

28

Imerican Journal OF OBSTETRICS AND GYNECOLOGY

TRANSACTIONS OF THE SEVENTY-FIRST ANNUAL MEETING OF THE AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

Editor in Chief
HOWARD C. TAYLOR, JR.

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Official Publication

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American Journal of Obstetrics and Gynecology

Editors Howard C. Taylor, Jr., Editor in Chief 622 West 168th St., New York 32, New York

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Allan C. Barnes, *Editor* 601 North Broadway, Baltimore 5, Maryland

Publisher The C. V. Mosby Company
3207 Washington Blvd., St. Louis 3, Missouri

Entered at the Post Office at St. Louis, Mo., as Second-Class Matter

Business Communications

Business Communications. All communications in regard to advertising, subscriptions, changes of address, etc., should be addressed to the publishers. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Missouri.

Subscription Rates. United States, its Possessions, and Canada \$15.00; Latin America and Spain \$16.50; Other Countries \$17.50. Students, interns, and resident physicians: United States, its Possessions, and Canada \$9.00; Latin America and Spain \$10.50; Other Countries \$11.50. Single copies \$2.50 postpaid. Remittances for subscription should be made by check, draft, post office or express money order, payable to this Journal.

Publication Order. The monthly issues of this journal form two semiannual volumes; the index is in the last issue of the volume—in the June and December issues.

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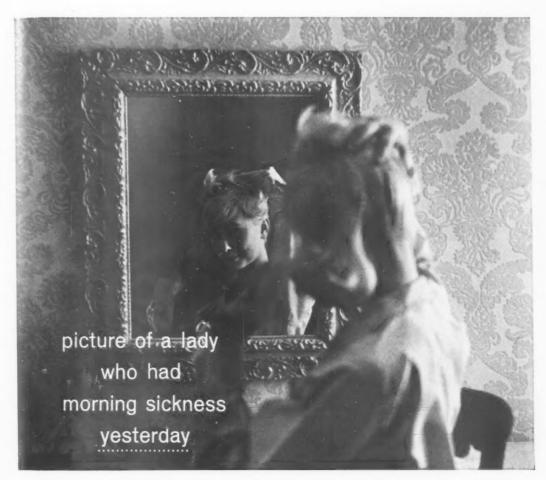


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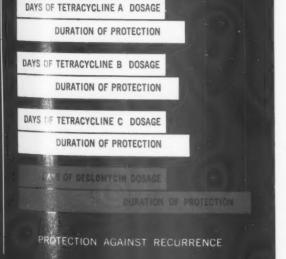
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PFIZER

uncomplicated

prevention of "next-morning sickness" with a single bedtime dose

Bonine®

BRAND OF MECLIZINE HYDROCHLORIDE

a record of effectiveness, excellent toleration, and economy



IN BRIEF

BONINE (meclizine hydrochloride) is the dihydrochloride of 1-p-chlorobenzhydryl-4-m-methylbenzylpiperazine, an antihistaminic-anticholinergic compound for prevention and relief of nausea and vomiting due to a variety of causes.

INDICATIONS: Valuable in the symptomatic relief of nausea and comiting of pregnancy. Also endicated for motion sickness, radiation sickness,

vertiga associated with Ménière's syndrome, labyrinthitis. Fenestration procedures, vestibular dysfunction, and dizzinos associated with cerebral arteriosclerosis.

ADMIN TRATION AND DOSAGE: For control of nausea and vomiting of pregnancy, a single dose of 25 to 50 mg. at bedtime is usually effective. For dosage schedules in other indications, see package insert.

SIDE EL ECTS: Not a phenothiazine, the side effects reported in association with bonine have been uncompli-

cated, mild and/or transient and consist of occasional drowsiness, dryness of the mouth, and blurred vision. There are no known contraindications to BONINE.

PRECAUTIONS: As with other antihistaminic compounds, the physician should inform patients of the need for caution in driving a car or when engaged in other activities requiring alertness,

SUPPLIED: BONINE Tablets, scored, tasteless, 25 mg. BONINE Chewing Tablets, mint-flavored,

25 mg. BONINE Elixir, cherry-flavored, 12.5 mg. per teaspoonful (5 cc.).

only rarely does one drug meet so well the needs of one condition

More detailed professional information available on request,



PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, N.Y. / Science for the world's well-being Pfizer





What do you look for in a prenatal supplement, Doctor? Calcium, of course, and iron, as well as the essential vitamins and minerals. (With new Pramilets, you get: a good supplemental dosage of phosphorus-free calcium plus important iron-férrous fumarate-plus all the other necessary nutrients.) What does your pregnant patient look for in a prenatal supplement? Convenient dosage? A tablet she can swallow? A pretty bottle for her dresser? Make it Pramilets. then. She gets them all—and you

get a formula that will carry her through term. Pramilets, in graceful Table Bottles of 100 Filmtabs.

> New Pramilets: Comprehensive vitamin-mineral support with just one Filmtab _ daily.



March, 1961

iec.

Page 21

IF YOUR OWN WIFE WERE A SPONTANEOUS ABORTER ... WHAT WOULD YOU DO, DOCTOR?

1,425 physicians answered this question by treating abortion-prone women in their own families with Hesper-C Prenatal. 1,248 successful pregnancies (87.6%) resulted.'

Fetal salvage rates as high as 95% have been achieved when hesperidin complex and ascorbic acid (as provided by Hesper-C Prenatal) were administered with the usual vitamin and mineral supplementation.^{2,3}

Hesper-C Prenatal (hesperidin complex, ascorbic acid **plus** vitamin-mineral supplementation) provides an established therapy for the restoration and maintenance of capillary integrity. It thus helps protect the habitual aborter and every pregnant woman against the decidual bleeding and spontaneous abortion triggered by capillary fragility.

1. Reports on file at The National Drug Company; data available on request. 2. Javert, C.: Obst. & Gynec. 3:420, 1954. 3. Greenblatt, R. B.: Obst. & Gynec. 2:530, 1953.

Hesper-C Prenatal

a **precaution** in every pregnancy a **necessity** in habitual abortion







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for Dramatically better management of obstetrical procedures

AMSCO "800" OBSTETRICAL TABLE

... so completely fresh in its design approach as to be truly revolutionary in its convenience and control for operative as well as perineal route delivery.

- narrow, flowing lines
- permanent or portable power base (or new Anesthesia Distribution base)
 - fingertip controls
 - retractable foot section
 - extendible 12" delivery shelf
 - ratchet type legholder sockets
 - flexible head and foot sections





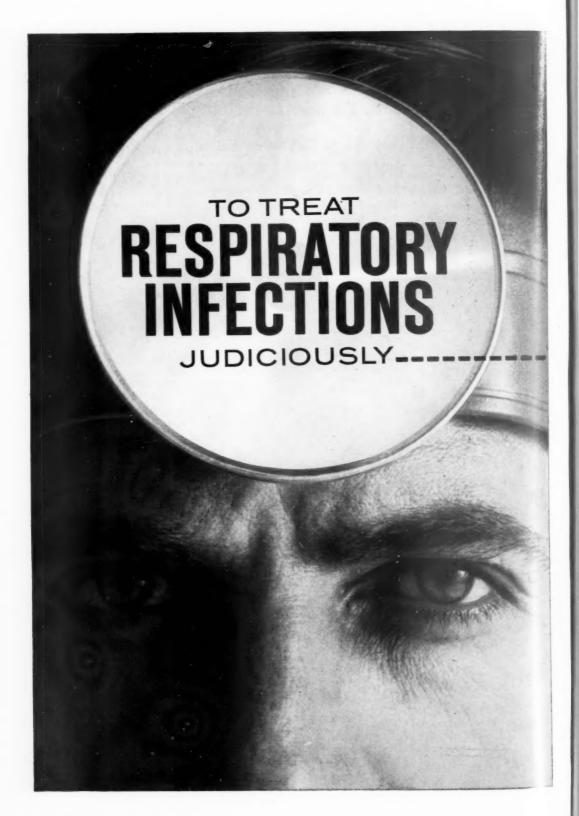
World's largest designer and manufacturer of Sterilizers, Surgical Tables, Lights and related hospital equipment

· Write for these two NEW, fully illustrated brochures:

AMSCO OBSTETRICAL TABLES TC-224-R1 AMSCO HOSPITAL LIGHTING LC-121-R1

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- . . . so advanced in its suspension, positioning and optical system as to establish new standards for obstetrical illumination.
 - · absorbs heat-producing infrared rays
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 - adaptable to all ceilings
 - dual control of light head . . . by circulating personnel or by obstetrician through patented sterilizable control handle



When it's penicillin-susceptible and the patient is not allergic **Use an orally maximal penicillin**

potassium phenethicillin

Consistent dependable therapeutic response through maximal absorption, maximal serum concentration and longer duration of inhibitory antibiotic levels for less susceptible organisms,

Available as Maxipen Tablets, 125 mg. and 250 mg.; Maxipen for Oral Solution, 125 mg. per 5 cc. of reconstituted liquid.

Literature on request

---or----

When you hesitate to use penicillin (eg. possible bacterial resistance or allergic patient)

You can count on



Extends the Gram-positive spectrum of usefulness to include many staphylococci resistant to one or more of the commonly used antibiotics—narrows the spectrum of side effects by avoiding many allergic reactions and changes in intestinal bacterial balance.

Available as Tao Capsules, 250 and 125 mg.; Tao Oral Suspension, 125 mg. per 5 cc.; Tao Pediatric Drops, 100 mg. per cc. of reconstituted liquid; Intramuscular or Intravenous as oleandomycin phosphate. Other Tao formulations also available: Tao®-AC (Tao, analgesic, antihistaminic compound) Tablets; Taomid® (Tao with Triple Sulfas) Tablets, Oral Suspension.

Literature on request

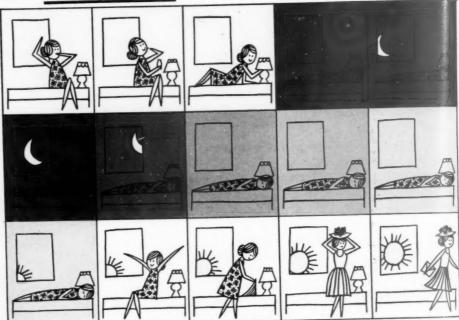
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Formulated from Pfizer's line of fine pharmaceutical products



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BENDECTIN

at bedtime ~



prevents morning sickness here! ". [Be

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Benty Decap Pyride

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"... I have gained the best results with [Bendectin]... Because these tablets have a protective coating... the dose taken at night becomes effective in the morning."

NEW DOUBLE-BLIND STUDY SHOWS BENDECTIN EFFECTIVE IN 94% OF PATIENTS²

Medication	Number of patients	Complete relief	Failure			
Bendectin	52	23 (44%)	26 (50%)	3 (6%)		
		TOTA				
Placebo	57	13 (23%)	24 (42%)	20 (35%)		
		TOTA	13.1365			

"Bendectin was administered in a preliminary study to 146 patients and later, in a controlled, double-blind study to 52 patients, or to a total of 198 patients suffering from nausea and vomiting of pregnancy. A very gratifying therapeutic response was obtained in 178 or 90 per cent. In a double-blind portion of this study, the response of 52 patients treated with Bendectin was compared with that of 57 other patients treated with a placebo. In this group of 109 patients, there was a favorable response to Bendectin in 94 per cent and to the placebo in only 65 per cent."

Measure Bendectin against your present Rx:

Q. Has your present Rx been shown to relieve morning sickness — before it starts — in more than 9 out of 10 patients?²⁻⁵

Q. Is your present Rx free of phenothiazine-like side effects and habituating properties?

Q. Is it economical? Does it cost less per day, for example, than a quart of milk?

With Bendectin, the answer to all three is YES.

FORMULA:

DOSAGE: Two tablets at bedtime.

SUPPLY: Bottles of 100 and 500.

1. Middleton, T. F.: Postgrad. Med. 24:699, 1958.

Geiger, C. J., et al.: Obst. & Gynec. 5:688, 1959.
 Nulsen, R. O.: Ohio State M. J. 53:665, 1957.

4. Personal communications, 1956-57.

Fersonal communications, 1956-57.
 Towne, J. E.: Internat. Rec. Med. 171:583, 1958.

TRADEMARKS: BENDECTING, BENTYLO, DECAPRYNO



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THE HEMATINIC WITH **BUILT-IN** NUTRITIONAL SUPPORT...











Women of menstrual age, many growing children, blood donors, geriatric patients and convalescents may need a hematinic . . . and all can benefit from Livitamin.

Livitamin offers the ideal formula to restore depleted iron reserves and give nutritional support—an important aspect of iron deficiency.

Iron in Livitamin is well absorbed and stored and well tolerated. B complex and other ingredients provide integrated nutritional support.



And Livitamin is a boon for your taste-fussy patients who *should* but *will not* take a hematinic.

LIVITAMIN

the hematinic with built-in nutritional support

FORMULA: Each fluidounce contains:

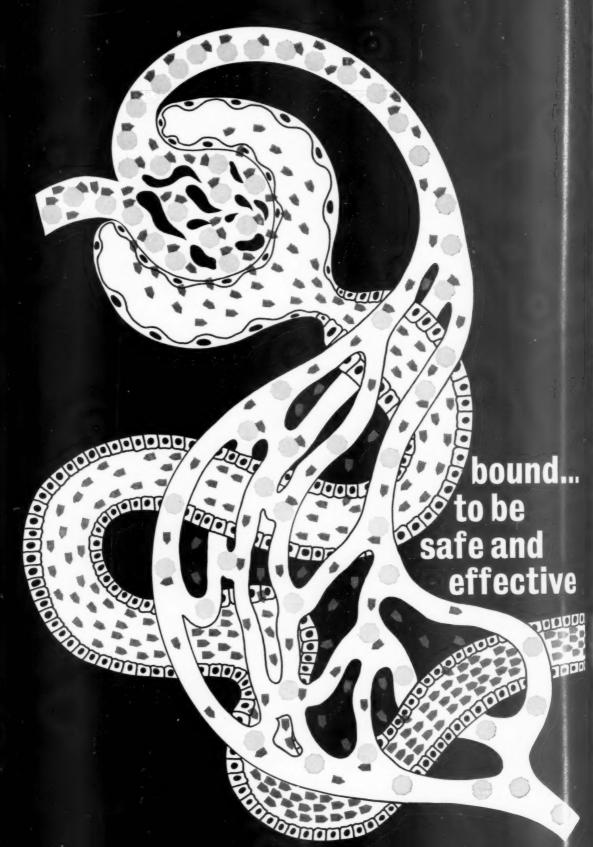
Iron peptonized			420 mg.	
Iron peptonized (equiv. in elemental iron to 71 mg.) Manganese citrate, soluble, N.F.			158 mg.	
Thiamine hydrochloride			10 mg.	
Riboflavin			10 mg.	
Cobalamin			20 mcg.	
Nicotinamide				
Pyridoxine hydrochloride				

Pantothenic acid.	0	0	0		0	0		0	5 mg.
Liver fraction 1									2 Gm.
Rice bran extract			•						1 Gm.
Inositol									30 mg.
Choline									60 mg.

SUPPLIED: Liquid or capsule; also available as capsules, LIVITAMIN with Intrinsic Factor.

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco



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SUPPLIED
per 5 cc.
*Conserva

REFERI CE. 1959. 2 C. al.: Are J. M., Jr. J. Urol., Pali in any urinary tract infection: "it is the kidney which is the most important consideration"... "In ections limited to the lower urinary tract ar comparatively rare"2

In the bloodstream, free FURADANTIN and FURADANTIN bound to plasma proteins are in quilibrium Free FURADANTIN passes readily through the glomerular filter. Protein-bound FURADANTIN, however, is not filtered by the glomerulus and reaches the peritubular capillaries. Here equilibrium is restored, and the FURADANTIN released from its bound state diffuses through the interstitial spaces and is secreted by the tubular cells. Exacting studies "suggest a three-component system for the renal transport of nitrofurantoin. That is, this nitrofuran appears to be filtered at the glomeruli and both secreted and reabsorbed by the tubules."3

Furadantin safeguards the kidney via a "threecomponent system of renal transport"3 . . . insuring continuous, intimate contact with functioning renal tissue

For more than 8 years . . . in over 8,000,000* courses of treatment . . . a distinguished record of safety and efficacy

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... may be given for extended periods of time without development of side effects or of drugresistant mutants."4

"... was given continuously and safely for as long as three years."5

AVER GE FURADANTIN ADULT DOSAGE: 100 mg. tablet q.i.d.

with neals and with food or milk on retiring.

SUPPLIED: Tablets, 50 and 100 mg.; Oral Suspension, 25 mg.

per 5 cc. tsp.

*Conservative estimate based on clinical use since introduction.

REFERE CES: 1. Thompson, I. M.: Family Physician, Chicago 9:14, 1959. Campbell, M. F.: Mod. Med. 24:85, 1956. 3. Paul, M. F., et al.: Am J. Physiol. 197:580, 1959. 4. Johnson, S. H., III, and Marshall,

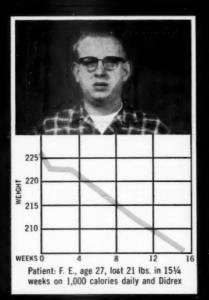
M., Jr. J. Urol., Balt. 82:162, 1959. 5. Lippman, R. W., et al.: J. Urol., Falt. 80:77, 1958.

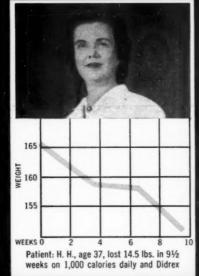


EATON LABORATORIES

Division of The Norwich Pharmacal Company

NORWICH, NEW YORK







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UPJOHN ANNOUNCES



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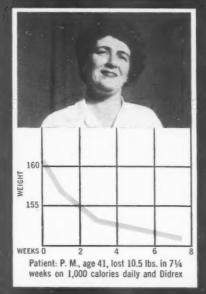
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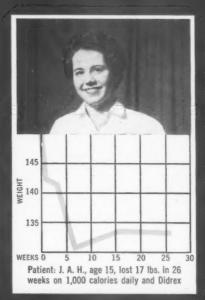
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References:
(Didrex.).
2. Oster. I appetite su A controlle (February)







WEEK AFTER WEEK

in obesity management Put it to your patient this way: The basic therapeutic objective of obesity management is to change dietary habits built over

months or years of weight accumulation. This takes time and will. Consider Didrex, the new Upjohn appetite suppressant. Happily, it elevates mood which makes dieting more acceptable. More important, it works: "persistent significant weight loss" in patients followed for as long as 20 weeks. Added to your favorite reducing regimen, ½ to 1 Didrex tablet one to three times daily is usually adequate to preclude the "weight plateau" that so often discourages dieters after a few weeks. Available as 50 mg. tablets in bottles of 100.

The Upjohn Company, Kalamazoo, Michigan

Photos and case histories courtesy Drs. Alan S. Rubenstein, P. V. Dilts and William Conroy, Springfield, Illinois

Trademark - brand of benzphetamine hydrochloride, UPJOHN

References: 1. Stough, A. R.: Weight loss without diet worzy: use of benzphetamine hydrochloride (Didrexes). Journal of the Oklahoma State Medical Association, 53:760-767 (November) 1960. 2. Oster. H., and Medlar, R.: A clinical pharmicologic study, of benzphetamine (Didrex@s, a new appetite suppressant. Arizona Medicine, 77:398-404 (July) 1960. 3. Simkin, B., and Wallace, L.: A controlled clinical trial of benzphetamine (Didrex@s). Current Therapeutic Research, 2:33-38 (Pchruary) 1960.

BRIEF BASIC INFORMATION

Description: Didrex is the Upjohn brand of benzphetamine hydrochloride $[(+)-N-benzyl-N,\alpha-dimethyl-phenethyl$ amine hydrochloridel. A sympathomimetic compound with marked anorectic action and relatively little stimulating effect on the CNS or cardiovascular system.

Indications: Control of obesity.

Contraindications: None known to date. However, use with caution in moderate or severe hypertension, thyrotoxicosis, acute coronary disease, or cardiac decompensation.

Dosage: Initiate appetite control with 1/2 or 1 tablet (25 to 50 mg.) in midmorning for several days. Then adjust dosage to suit each patient's need to a maximum of 3 tablets daily (150 mg.). Side Effects: No effects on blood, urine, renal or hepatic functions have been noted. Minimal side effects have been observed occasionally: dry mouth, insomnia, nausea, palpitations and nervousness.

Supplied: 50 mg., press-coated, scored tablets, in bottles of 100.

TRICHOMONADS EXPLODE



- 1. VAGISEC liquid and jelly penetrate and dissolve vaginal mucus, exposing even deeply embedded trichomonads.
- VAGISEC's three active ingredients* permeate the cell's membrane, remove waxes and lipids, denature proteins.
- 3. Water is forced through the weakened cell wall, causing trichomonad to swell and explode. All within 15 seconds of contact.

Specific therapy for vaginal trichomoniasis VAGISEC® liquid and jelly. "Many other chemicals stop motion and we have assumed that the organisms are dead, but with [VAGISEC] there can be no doubt, since only fragments remain."

The first office treatment with VAGISEC brings immediate symptomatic relief. With the very first office treatment, Decker² achieved immediate relief of acute symptoms in all 64 cases of acute trichomoniasis studied.

Cure rates as high as 96% with VAGISEC confirmed by negative cultures for three consecutive months. Roberts and Sullivan³ successfully treated 96% (48 of 50) vaginal trichomoniasis patients with VAGISEC, all of whom remained flagellate free, as proved by repeated negative cultures for three months after treatment. Giorlando and Brandt,⁴ and Weiner⁵ were equally successful with VAGISEC, curing 93.1% (54 patients of 58), and 90.2% (46 patients of 51) respectively, by means of the VAGISEC technique.

To prevent re-infection—RAMSES® for the husband. As Romney® points out, "... therapy which is directed solely towards the female patient is unrealistic and ineffectual." Husbands readily cooperate when you prescribe RAMSES, the prophylactic with "built-in" sensitivity.

References: 1. Davis, C. H.: West. J. Surg. 63:53 (Feb.) 1955.
2. Decker, A.: New York J. Med. 57:2237 (July 1) 1957. 3.
Roberts, C. L., and Sullivan, J. J.: West. Med. 1:12 (Apr.) 1960.
4. Giorlando, S. W., and Brandt, M. L.: Am. J. Obst. & Gynec. 76:666 (Sept.) 1958. 5. Weiner, H. H.: Clin. Med. 5:25 (Jan.) 1958. 6. Romney, S. L.: M. Sc. 8:235 (Aug. 25) 1960.
VAGISEC and RAMSES are registered trade-marks of Julius Schmid. Inc.

VAGISEC and jelly

*Active ingredients in Vagisec liquid: Polyoxyethylene nonyl phenol, sodium ethylene diamine tetra-acetate, sodium dioctyl sulfosuccinate. In addition, Vagisec jelly contains alcohol 5% by weight.

Julius Schmid, Inc. 423 West 55th Street New York 19, N. Y.

XYLOCAINE® LOCAL ANESTHETIC



In the final analysis, only clinical experience can assure the survival of a drug. It is therefore gratifying to know that the performance of Xylocaine, in both dentistry and medicine, appraised in the light of current findings, confirms the original observations made more than a decade ago. Xylocaine has stood the test as a reliable and highly effective local anesthetic.

Surgery: infiltration nerve block and topical

Xylocaine is well suited for infiltration and nerve block techniques for a large number of major and minor operative procedures. Xylocaine gives anesthesia of adequate duration, is fast acting with high diffusibility, and its action is predictable. Minimal dosage consistently produces profound anesthesia. The margin of clinical safety is wide, and side effects, considering the extensive use of Xylocaine, are rare. For infiltration, 0.25% and 0.5% solutions are used in volumes of 30 cc. to 100 cc. The 1% solution may be used when smaller volumes of 10 cc. to 30 cc. are to be administered. When a single injection of Xylocaine is used for peridural, spinal and other



major nerve blocks, the concentration and volume varies with the type of block and the individual requirements. The total dosage of Xylocaine should not exceed 500 mg. when administered with epinephrine, or 300 mg. without epinephrine. Xylocaine is one of the very few local anesthetic agents which are effective topically as well as by injection. This is an important advantage in many surgical procedures where mucous membranes of the respiratory, upper gastrointestinal and lower genitourinary tracts, the eye and ear, and the anoreetal area are involved. The 2% and 4% concentrations of Xylocaine solutions are used for topical anesthesia. Volumes are adjusted according to the requirements of the surgical procedures being undertaken.

Obstetrics, gynecolog Ja la caudal, spinal "saddle bloomegen is

Spotty anesthesia, once a major dra vast in or a peridural and caudal techniques, occurs a sy be a rarely with Xylocaine because of its high a is veretically with Xylocaine because of its high a is veretically the index, wide diffusibility, short late testhes a period, and adequate duration of nerve blocause of Its relative safety and reliability of performance has caused Xylocaine to be called a stissue a drug of choice for extradural analgesia ssesses a Because of the specific dosage requirem testhesial for extradural anesthesia, two strengts th cotton Xylocaine, 0.8% and 1.2% are packaged in stillation cc. single dose containers. Operative analgate a surfact is obtained with volumes of 25 cc. to 30 cc. so or term



ualize v 0.8% Xylocaine HCl. Concentrations of I 2% have been used for peridural anesth where complete muscular relaxation is tration quired; this condition can, in many instar be achieved with Xylocaine HCl 1.2%. "X caine spinal" may be used with predict leally results for obstetrical, gynecological and tions a logical procedures, and for surgery of the ation n v retrob abdomen and the lower extremities. Xylor spinal" has a low binding affinity that mizes potential nerve injury. Its anest leation effect is routinely rapid, profound, well its, abra ated and free from "spottiness." It is tet lary 3 pletely stable in the presence of spinal setable at The anesthetic action of "Xylocain spins salgia, in of moderate duration, averaging 100 minuts, and y followed by another 40 minutes of analy traum, ti e ieral use:injectable Da id topical anesthesia

le gen al practitioner, the internist, and the rgeon like are frequently called on to relieve air in or rform minor surgical procedures that accessfully managed with the aid of har is ver tile anesthetic. Consistently effective ater jesther a may be expected from Xylocaine bla cause f its fast and profound action and rio reading ability. It is virtually nonirritating a tissue and is relatively nonsensitizing, and esia ssesse a wide margin of safety. For topical rema esthes a Xylocaine may be applied as a spray, gths the cotion swabs, or by packs, as well as by ed in stillation into a cavity and by application nale to a surface. Local anesthesia of nerves, plex-30 cc es or terminal nerve endings requires indi-



volumes and concentrations. For eral u Xylocaine is recommended in conof 0.5%, 1% and 2%, with the solut n generally used for nerve block. limal · lumes of 4% Xylocaine may be used those cases where lower concentions a ineffective or inadequate. The 4% tion n y also be used transtracheally and retrob bar injection.

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for topical application: Laceraas, abra ons, burns, corneal analgesia, ineet lary goscopy, pruritus. Indications for ctable : esthesia : suturing, wound closure, Balgia, linor surgery, removal of moles, on miles, and ysts, fracture reduction, bursitis, anal traum ic syndrome, herpes zoster.



Astra Pharmaceutical Products, Inc.





For Infiltration and Nerve Block Maylocaine HCl 0.5% and 1% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials. Xylocaine HCl 2% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials; also 2 cc. ampules (10's and 30's).

For Spinal Anesthesia ■ Xylocaine HCl 5% with glucose 7.5% (specific gravity 1.030-1.035) in 2 cc. ampules (10's and 100's).

For Peridural Anesthesia Xylocaine HCl 0.8% and 1.2% without and with epinephrine 1:200,000 in 30 cc. single dose containers. For Continuous Peridural Anesthesia Xylocaine HCl 1% without epinephrine in 100 cc. single dose containers.

For Transtracheal Use and For Retrobulbar Injection • Xylocaine HCl 4% without epinephrine in 5 cc. ampules (10's).

For Topical Application Xylocaine HCl 0.5% and 1% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials. Xylocaine HCl 2% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials; also 2 cc. ampules (10's and 30's). Xylocaine HCl 4% without epinephrine in 50 cc. screw-cap bottles. (NOTE: This dispensing form is never to be used for injection.) Also available for topical use, Xylocaine Ointment 2.5% and 5%, Xylocaine Jelly 2%, and

Xylocaine Viscous 2%.
Write for additional complete information concerning specific Xylocaine usage.

\$Bryce-Smith, R.: Local analgesic drugs, Brit, M.J. 1:1039 (April 2) 1960.

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when your diagnosis is menopause...

consider that current medical opinion favors treatment

"I know that many physicians feel that the menopause is a physiological process and no therapy for it is indicated.... I do not belong to this school of thought, though therapy can certainly be overdone. We have to bear in mind, I think, that flushes

are merely one aspect of the menopause; irascibility, migrainoid headaches, insomnia, apprehension, moods of depression and nervousness may occur without any hot flushes at all. Then we mustn't forget the sequelae of the menopause, such as senile vaginitis, pruritus vulvae, and osteoporosis. These must be considered part of the menopausal syndrome."*

*Transatlantic Telephone Symposium, The Effect of Estrogens in the Menopause, Amsterdam/New York, 1959. Transcript available on request.

in the menopause—there is no substitute for a specific

"Premarin" the natural oral estrogen that imparts a "sense of well-being"

Usual dosage: 1.25 mg, daily. Increase or decrease as required. Cyclic therapy is recommended (3 week regimen with 1 week rest period) to avoid continuous stimulation of breast and uterus.



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in constipation whenever stool softening is all that's needed for normal evacuation



in cardiac patients
avoid straining



in obstetric patients avoid peristaltic stimulation



in pediatric patients
avoid hard stools

GOLAGE Dioctyl sodiam gulfosuccinate, Mead Johnson

achieves evacuation without laxative action

Because Colace achieves natural, easy evacuation by stool-softening action alone, it is ideally suited to the relief of constipation whenever peristaltic stimulation is unnecessary or undesirable.

Therapy with Colace has proved particularly useful in correcting constipation

during pregnancy¹ and the postpartum period²...in pediatric patients, often with the additional problem of chronic fecal impaction³...in infancy⁴...and in cardiac patients.⁵

supplied: Colace Capsules (50 mg. and 100 mg.), bottles of 30, 60, and 250. Colace Liquid (1% solution, 10 mg. per cc.), bottles of 30 cc., with plastic 'Safti-Dropper' calibrated for 1 cc. Colace Syrup (20 mg. per teaspoon), bottles of 8 fl. oz.

references: (1) Antos, R. J.: Southwestern Med. 37:236-237, (April) 1956. (2) Schoenfeld, R. C.: Am. J. Obst. & Gyncc. 74:1114-1115 (Nov.) 1957. (3) Feigen, G. M.: Calif. Med. 86:41-43 (Jan.) 1957. (4) Towsley, H. A.: J. Michigan M. Soc. 54:1064-1066, 1138 (Sept.) 1955. (5) Smigel, J. O.; Lowe, K. J.; Hosp, P. H., and Gibson, J. H.: M. Times 86:1521-1526 (Dec.) 1958.



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Symbol of service in medicine

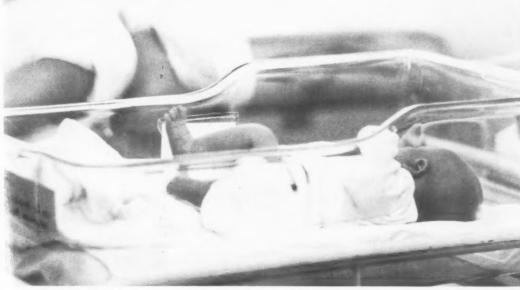
Why do 86% of pediatricians prefer evaporated milk for formula feeding?

Proven nutritional value!

Readily diluted and supplemented for the infant's changing needs, the evaporated milk formula fulfills the nutritional requirements of most infants from birth throughout infancy. A proven history of successful feeding makes evaporated milk the most widely used form of milk for infant feeding today.

Carnation's position of responsibility and leadership in the specialized field of infant feeding is important in the choice of formula milks. This is the milk used in more hospital formula rooms throughout the world than all other brands combined.

- Permits the doctor to prescribe for the baby's changing needs
- · Curd tension zero
- · Digestible, uniform, safe
- · Low incidence of allergy
- · Simple to prepare





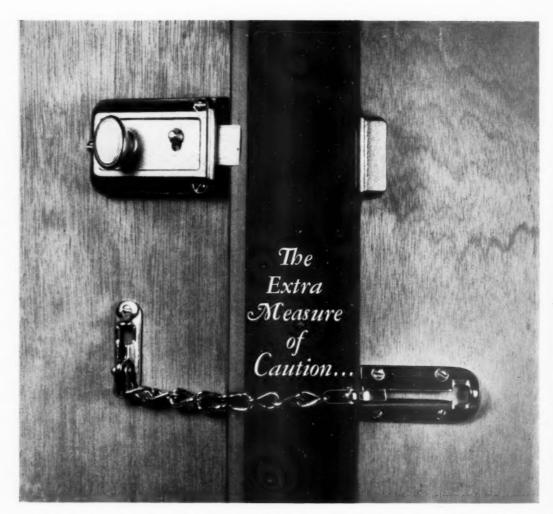
WORLD'S LEADER BY FAR, FOR INFANT FORMULA FEEDING

"from Contented Cows"

THE READY-PREPARED EVAPORATED MILK FORMULA

Carnalac is Carnation Evaporated Milk with its added Vitamin D, plus carbohydrate. The mother just adds water. Diluted 1:1, Carnalac provides 20 calories per fluid ounce.





Tetracycline now combined with the new, more active antifungal antibiotic-Fungizone-for broad spectrum therapy/antimonilial prophylaxis

A new advance in broad spectrum antibiotic therapy, MYSTECLIN-F provides all the well-known benefits of tetracycline and also contains the new, clinically proved antifungal antibiotic, Fungizone. This Squibb-developed antibiotic, which is unusually free of side effects on oral administration when given in oral prophylactic doses, has substantially greater in vitro activity than nystatin against strains of Candida (Monilia) albicans.

Thus, in addition to providing highly effective broad spectrum therapy, MYSTECLIN-F prevents the monilial overgrowth in the gastrointestinal tract so commonly associated

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New Mysteclin-F provides this added antifungal protection at little increased cost to your patients over ordinary tetracycline preparations.

Available as: MYSTECLIN-F CAPSULES (250 mg./50 mg.) MYSTECLIN-F HALF STRENGTH CAPSULES (125 mg./25 mg.) MYSTECLIN-F FOR SYRUP (125 mg./25 mg. per 5 cc.) MYSTECLIN-F FOR AQUEOUS DROPS (100 mg./20 mg. per cc.)

For complete information, consult package insert or write to Professar sional Service Department, Squibb, 745 Fifth Avenue, N. Y. 22, N.

MYSTECLIN-F
Squibb Phosphate-Potentiated Tetracycline (SUMYCIN) Plus Amphotericin B (FUNGIZON

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"MYSTECLIN", "SUMYCIN" AND "FUNGIZONE" ARE SQUIBE TRADEMARKS

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standard
for
cytodiagnosis



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After episiotomy

What now?



for one thing

THE SUPERIOR SYSTEMIC ANTI-INFLAMMATORY ENZYME

to control inflammation, swelling, and pain in EPISIOTOMIES, pelvic inflammatory disease, postpartum breast engorgement, thrombophlebitis.

Chymar reduces inflammation and edema of tissues, hastens absorption of blood extravasates, diminishes pain, and thus promotes smoother healing. More than 80% of episiotomies have shown complete relief of edema in the wound, and in no case was it necessary to release sutures.1 Chymar also reduces pain and engorgement in the postpartum breast.2 In pelvic inflammatory disease, Chymar has reduced inflammation, swelling and pain in 85% of patients.3 And in thrombophlebitis, Chymar rapidly diminishes pain, swelling and tenderness around the vein; allows earlier activity of the patient.4

1. Fullgrabe, E. A.: Ann. New York Acad. Sc. 68:192, 1957. 2. Clinical Reports to the Medical Department, Armour Pharmaceutical Company, 1960. 3. Reich, W. J., and Nechtow, M. J.: Am. Pract. & Digest Treat. 11:45, 1960. 4. Teitel, L. H.; Siegel S. J.; Tendler, J.; Reiser, P., and Harris, S. B.: Indust. Med. &

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Chymar Aqueous and Chymar (in oil) contain chymotrypsin, a proteolytic enzyme with systemic anti-inflammatory and anti-dematous properties. ACTION: Reduces inflammation of all types; reduces and prevents edema except that of cardiac orrenatorigin, hastens absorption of blood and lymph extravasates; restores local hastens absorption of blood and lymph extravasates; restores local circulation; promotes healing; reduces pain. INDICATIONS: Chymar is indicated in respiratory conditions to liquefy thickened socretions and suppress inflammation of mucosa and bronchiolst issue; in accidental trauma to speer feduction of hematoms and edema; in inflammatory dermaloses to ameliorate acute inflammation in conjunction with standard therapies; in gynecologistic conditions to suppress inflammation and edema and stimulate healing; in surgical procedures to minimize surgical trauma with inflammation and swelling; in genito-uniary disorders to reduce pain and promote faster resolution; in ophthalmic and otorhinch arryngic conditions to leasen hematoma, edema and inflammatory changes; in dental procedures to lessen pain and gum tissue trauma, with inflammation and swelling, in reaction to extractions or surgery. PRECAUTIONS: Chymar Aqueous are for intramuscular injection only. Although sensitivity to chymotrypsin is uncommon, allergic or anaphylactic reactions may occura will any lorsing protein. The usual remedial agents should be read in the common of the surgery of th any foreign protein. The usual remedial agents should be read ... available in case of untoward reaction. Precautions (scratch te-ing for Chymar, scratch or intradermal testing for Chymar Aqueou should be exercised in those patients with known or suspect allergies or sensitivities. DOSAGE: 0.5 cc. to 1.0 cc. deep into muscularly once or twice daily, depending on severity of conditions. Decrease frequency as course of condition is altered. In chrol-or recurrent conditions, 0.5 cc. to 1.0 cc. once or twice week SUPPLIED: 5 cc. vials, 5000 Armour Units of proteolytic activ

O Jan. 1961, A.P. Co.

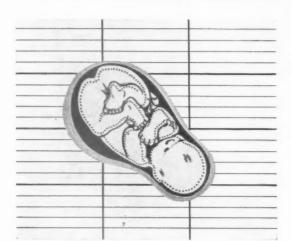


now in threatened premature delivery

Dactil-OB

maintains gestation / increases fetal survival rate

Brand of piperidolate hydrochloride, hesperidin complex and vitamin C



"Dactil has been used as a preventive measure with great success and with no untoward effects."

In a study of 618 pregnancies over a period of 4 years, premature births were reduced from 13.1% of 168 patients without Dactil to 4.7% of 450 patients with Dactil.² In the treated patients birth weights were increased.

Dosage: 1 tablet q.i.d. from the beginning of pregnancy in any patient with a history of previous difficulty. For more information send for Dactil-OB brochure.

(1) Stephens, L. J.: Prevention of Premature Delivery: Am. J. Obst. & Gynec. 70:6 (June) 1958. (2) Stephens, L. J., in press.



yn c.

In trichomonas vaginitis "... permanent CURES in 84.6%" = "... symptomatic and bacteriologic CURES" in 100%2 = "symptomatic CURE was obtained in 100%, and bacteriologic CURES in 82.5%"3 in moniliasis "symptomatic CURE was effected in about 80%"4 in mixed infections "complete symptomatic and bacteriologic **CURES** in 92%"3 in endocervicitis 75% "were clinically and bacteriologically (as indicated by vaginal smears and cultures) CURED"5

STOPS THE TORMENT DESTROYS THE CAUSE

Vaginitis (trichomonal, monilial, nonspecific), Cervicitis

References: 1. Angelucci, H. M.: Am. J. Obst. & Gynec. 50:336, 1945. 2. Hensel, H. A.: Postgrad. Med. 8:293, 1950. 3. Cortese, J. T.: Clin. Med. 2:45, 1955. 4. Dill, L. V., and Martin, S. S.: M. Ann. District of Columbia 17:389, 1948. 5. Horoschak, A., and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946.



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Rx the anorexic with no reported contraindications

TENUATE suppresses appetite with no effect on heart rate, blood pressure, pulse or respiration, no alteration of BMR.²

In a recent study of 105 patients who used diethylpropion (TENUATE) throughout their pregnancies, the following effects on weight were recorded:

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SUPPLIED: TENUATE Tablets (25 mg. each), bottles of 100 and 1000; TENUATE DOSPAN Tablets (75 mg. each), bottles of 100.

REFERCES: 1. Alfaro, R. D.; Gracanin, V., and Schlueter, E.: J. Lancet, In press. 2. Huels, G.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 3. Nulsen, R. O.: Cur. Therap. Res. 2:102, 1960. 4. Horwitz, S.: Personal communication, 1959. 5. Spielman, A. D.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 6. Ravetz, E.: Michigan Acad. Gen. Pract. Symposium, 1959. 7. Decina, L. J.: Exper. Med. & Surg., In press. 8. Scanlan, J. S.: Personal communication, 1959. 9. Kroetz and Storck: Personal communication, 1959.

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(diethylpropion)

hunger control with less than 1% CNS stimulation^{2,49}



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NOW AVAILABLE—
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The better-tolerated ferrous fumarate is made available in optimal amounts at the sites where uptake is most efficiently accomplished. The bulk of the iron is timed for release through the duodenum-jejunum, and virtually all of the remainder in the ileum-thus corresponding closely to the normal sequence of absorption of medicinal iron described by Goodman and Gilman.²

The possibility of gastrointestinal irritation is greatly reduced...first, because of the excellent toleration of ferrous fumarate1, 3-6...second, because the concentration of iron salt is not unduly high at any one point.

Dioctyl sodium sulfosuccinate helps soften stools for easier elimination.

Each two-tone, green FERRO-SEQUELS capsule contains:

Ferrous fumarate

(equivalent to 50 mg. elemental iron) Dioctyl sodium sulfosuccinate

Bottle of 30.

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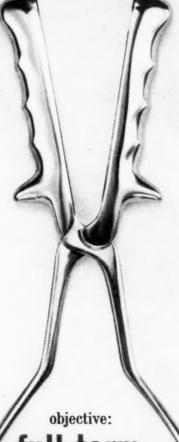
Bibliography—1. Feldman, H. S.: Ferrous Fumarate in the Treatment of Iron Deficiency Anemia. Virginia M. Month. 87:177 (April) 1960. 2. Goodman, L. S., and Gilman, A.: Pharmacological Basis of Therapeutics, Second Edition, Macmillan, New York, 1955, p. 1455. 3. Illingworth, D. G.: Ferrous Fumarate. Brit. M. J. II (5159):1099 (Nov. 21) 1959. 4. New and Nonofficial Drugs: Ferrous Fumarate. J.A.M.A. 171:1104 (Oct. 24) 1959. 5. Shapleigh, J. B., and Montgomery, A.: Ferrous Fumarate: A Clinical Trial of a New Iron Compound. Am. Pract. 10 (3):461 (Mar.) 1959. 6. Swan, H. T., and Jowett, G. H.: Treatment of Iron Deficiency with Ferrous Fumarate. Assessment by a Statistically Accurate Method. Brit. M. J. II (5155):782 (Oct. 24) 1959.

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threatened abortion

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Here are five reasons why:

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Brief Basic Information

			-	I. M.
0	Oral	Provera*	Depo-	Prover

	Oral Provera"	Debo-Provera
Description	Upjohn brand of medroxy- progesterone acetate.	Aqueous suspension, 50 mg. Provera per cc., for intramuscu- lar injection only.
Indications	Threatened and habitual abortion, infertility, dysmenorrhea, secondary amenorrhea, premenstrual tension, functional uterine bleeding.	Threatened and habitual abortion, endometriosis.
Dosage Threatened abortion	10 to 30 mg, daily until acute symptoms subside.	50 mg. I. M. daily while symptoms are present, followed by 50 mg. weekly through 1st trimester, or until fetal viability is evident.
Habitual abortion 1st trim.	10 mg. daily.	50 mg, I.M. weekly.
2nd trim.	20 mg. daily.	100 mg. l.M. q. 2 wks.
3rd trim.	40 mg. daily, through 8th month,	100 mg, I.M., q. 2 wks. through 8th month.
Supplied:	2.5 mg. scored, pink tab- lets, bottles of 25; 10 mg. scored, white tab- lets, bottles of 25 and	Sterile aqueous sus- pension for intra- muscular use only, 50 mg. per cc., in

Precautions: Clinically, Provera is well tolerated. No significant untoward effects have been reported. Animal studies show that Provera possesses adrenocorticoid-like activity. While such adrenocorticoid action has not been observed in human subjects, patients receiving large doses of Provera continuously for prolonged periodishould be observed closely. Likewise, large doses of Provera have been found to produce some instances of female fetal masculinization in animals. Although this has not occurred in human beings the possibility of such an effect, particularly with large doses over a long period of time, should be considered.

Provera, administered alone or in combination with estrogens, should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy has been eliminated.

†Each cc. of Depo-Provera contains: Medroxyprogesterone acetal 50 mg.; Polyethylene glycol 4000, 28.8 mg.; Polysorbate ϵ 1.92 mg.; Sodium chloride, 8.65 mg.; Methylparaben, 1.73 mg Propylparaben, 0.19 mg.; Water for injection, q.s.

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Propiomazine Hydrochloride, Wyeth

acts for 3-4 hours cuts recovery-room time

Predictable, short-acting Largon provides sedation that relieves apprehension and produces a light sleep. It enhances the action of analgesics and anesthetics, reducing the need for CNS depressants and extending the margin of safety. Its short action, similar to meperidine, permits repeat doses without overlapping effect. Also provides antiemesis. Largon has not been observed to produce maternal or fetal depression, jaundice or blood dyscrasias, or adverse cardiovascular effects.

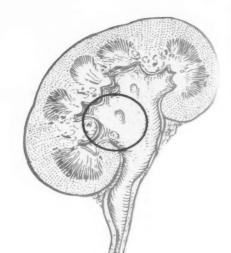
Supplied: Largon, 20 mg. per cc. in Water for Injection U.S.P., available in ampuls of 1 and 2 cc., packages of 25. For further information on prescribing and administering Largon, consult current Direction Circular enclosed with medication, or available on request.



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Urised combats bacteria while providing soothing relief in cystitis, urethritis, pyelitis, pyelonephritis, and prostatitis. Urised avoids toxic reactions or drug resistance.



as a first choice URISED is effective in 80 to 90% of urinary infections (no side effects reported)

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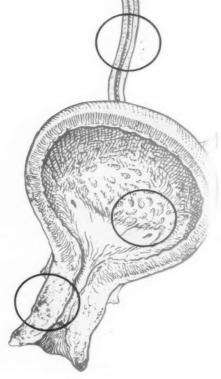
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March, 1961

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Page 53



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provide, in one tablet a day, ample amounts of the four basic vitamins and minerals needed to guard the well-being of your patient and her baby.

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*Traylor, J. B., and Torpin, R.: Am. J. Obst. & Gynec. 61:71-74 (Jan.) 1951.



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Soma's prompt relief of pain and stiffness can get your low-back patients back to work in days instead of weeks

Soma is unique because it combines the properties of an effective muscle relaxant and an independent analgesic in a single drug. Unlike most other muscle relaxants, which can only relax muscle tension, Soma attacks both phases of the pain-spasm cycle at the same time.

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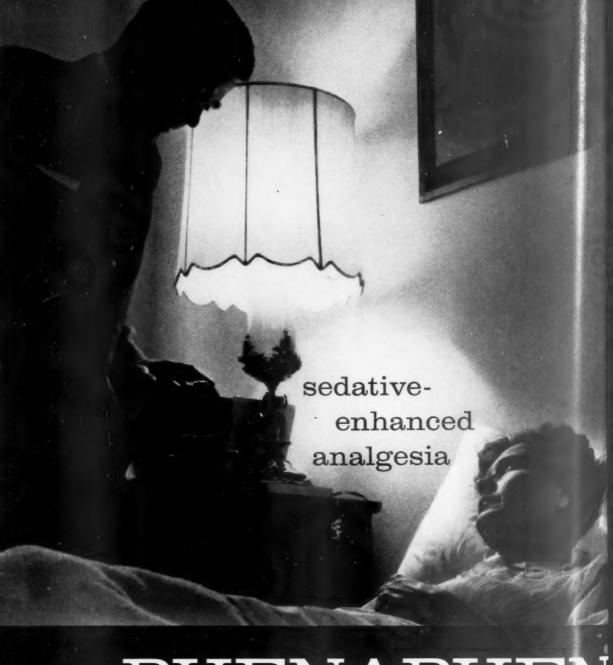
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I. Meyers. G. B.: Ind. Med. & Surg. 26:3, 1957. 2. Murray. R. J.: N. Y. St. J. Med. 53:1867, 1953. Bottles of 100 and 500 capsules.

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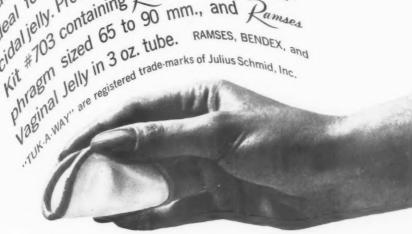
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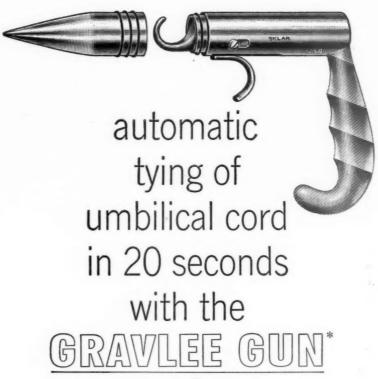
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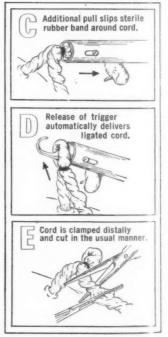


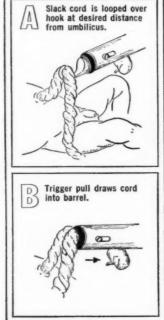
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1. Gravlee, L. C., and Jones, W. N.: Obst. & Gynec. 15:43 (Jan.) 1960. * U. S. PAT. NO. 2,942,604.

me



the 'teens-a time of transition

No longer a child, not yet a woman – surely the period of early female adolescence when your special counseling is needed. A word of advice to the youngster of menarche age may quiet her apprehensions and prepare her to accept all the important transitions of the female cycle. When your advice includes the use of Tampax®- the modern tampon method of protection — you are offering your patient, in addition, the reassurance of safe, complete, discreet menstrual hygiene.

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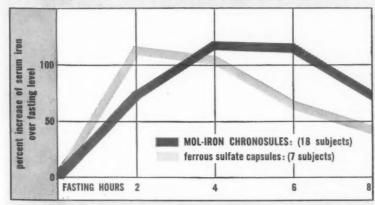
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American Journal of Obstetrics and Gynecology

Transactions of the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists

"... There are classes of men ..."

President's address

ROBERT A. ROSS, M.D.

Chapel Hill, North Carolina

More E than 30 years ago, during the process of organizing a completely new medical school, the dean would relieve the tedium and renew his vigor by ranging far and wide, seeking and acquiring articles for its library. One of the valued acquisitions was a full set of the *Transactions* of this Society.

While aiding in the organization of a new department of obstetrics and gynecology and awaiting the arrival of the new department head, I also sought sanctuary in this library. The availability of the *Transactions*, with its record of the works and lives of those who contributed to these volumes, has been a most fruitful experience in a life that has been abundantly rewarding. Thirty years ago

I was completely unmindful of the fact that a perusal of these *Transactions* would be obligatory for the preparation of this address. In fact I did not presume to associate myself with the organization in any way. I was fascinated by the reason for such a confederation: the motive, the desire, the inherent quality that assured success; knowing that the basis certainly was not selfishness. For a different reason and with the established fact of a different course, these founders have fascination; one is interested in learning "upon what meat doth this our Caesar feed that he has grown so great?"

A new president has wistful envy for an expression of gratitude found in an early address in another society: "Years ago, at a period in my professional history when I sorely needed a friend and a trusted counsellor, [the Society] sought me out upon the frontier and generously stepped forward and took me by the hand. Year by year she has

From the Department of Obstetrics and Gynecology, School of Medicine, University of North Carolina.

Presented at the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960.

guided and guarded me with the jealous care of a devoted mother. A year ago she placed upon my brow her jeweled crown and in my hand her symbolical wand. For all of this I have nothing with which to requite her in turn save my poor but hearty thanks." We have lost something by departing from such language. Certainly this age does not lack temerity. Conciseness and contractions are encouraged; humility is declared rather than allowed to become an ineffable manifestation of an indwelling quality. We find, however, a member who declined the nomination for presidency of the Association with a simple enunciated statement that the nomination was "unexpected, unsolicited, undesired, and undeserved." This was the generation of a hard-bitten general who declined the nomination for the presidency of the United States by declaring that he would not run for the office if nominated and would not serve if elected!

Such contemplation led in orderly sequence to a restudy of the events of the last quarter of the past century; political, military, socioeconomic, educational, scientific, and medical, both national and international. It was immediately evident that there are striking similarities between the decade of 1880 and our present time.

If we indulge in "then and now" recording, we find this country feeling the impact of war. It is not necessary to record our present unrest and uncertainty; in the '80's it was enormous. The Civil War was fought in our own country, not on some distant continent, destroying our own personal and community resources, decimating our own people and leaving the remainder benumbed when rightly they should have had an opportunity for abundant growth. It left over 600,000 dead men out of a young country's population of 31,500,000—larger than World Wars I and II combined. The South, with a population of 5,100,000 white, had 800,000 men in arms. There was a battle a day for 4 years—519 in Virginia, 298 in Tennessee, 19 in New Mexico, 6 in Minnesota, 6 in California, 4 in Oregon, 2 in Nevada, and one each in New York, Vermont, Illinois, Utah, Idaho, and Washington Territory.

At the outbreak of the war there were 300 young medical men from the South in training in Philadelphia alone. They immediately headed south on foot, by carriage, and by train to regroup in Richmond, Charleston, and New Orleans to receive further training. In similar fashion and in varying degrees medical education was disrupted throughout the nation. And the father of American gynecology was preoccupied with another war on another continent. Strong friendships and mutual respect are repeatedly mentioned in the early proceedings of our Society, formed and made more enduring by this starkly tragic war. There are wars and explosive potential today, yet medicine and medical thinking remain consistent and offer a common bond.

Among our founders are listed the youngest medical officer in the Confederate Army, a member of the U. S. Medical Cadets (a group of 100 young men destined for medical careers), and 3 who were prisoners of war but continued to function as doctors until exchange occurred. One was in the miserable Libby prison, but all the prisons were miserable and the death rate was terrifying: 180,000 Northern soldiers with 30,000 deaths; 200,000 Southern troops with 28,000 deaths.

This tragic mortality was not entirely due to enforced brutality or to a complete lack of sympathy. These medical officers found that the population of the South at this time used thorns for pins, used pokeberry juice for ink, scraped smokehouse floors and fish wharves for salt, saved urine for the nitrogen to make gunpowder, stripped trees for cinchona bark, and grew poppy seed for opium. A treatise on war surgery was printed on newspaper stock. Churchill said that it was the last war between gentlemen, albeit gentlemen who were beating each other's brains out.

The national economy, labor, industry, tariff, and exchange are intimately a part of politics and a play for politics. Again we find remarkable similarities.

The allegiances to industry and labor in the 1880's has a familiar arrangement. In from-

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ing our Constitution a prominent representative from Pennsylvania told the Federal Convention that the Senate must be "an aristocratic body," that "it must have great personal propriety; it must have the aristocratic spirit; it must love to lord it through pride." In the decade mentioned, it had become about what was suggested. In most states the major industry almost regarded the seat in the Senate as its right. The Knights of Labor also had words of admonition. They believed with Edmund Burke that "when bad men combine, the good must associate else they will fall, one by one, an unpitied sacrifice in a contemptible struggle." In the Midwest the newspapers commented that "many workers were affected with a malignant form of the eight-hour-day malady." These circumstances were the background for an incident of national importance, the Haymarket riot, and gave notoriety to a brilliant young surgeon; it also gave him the permanent label of "opportunist." Some years later it was incidental in impeachment charges before his County Medical Society. One of the counsellors was a member of our organization, as was the acting chairman. The surgeon was vindicated. He was a member of our Association.

The vicuna coat, deep freezers, and five percenters are not new symbols of political graft and skulduggery. In the other era being discussed we find the game being played for even higher stakes. The Crédit mobilier, the rum ring, the commodity bosses reached into high places with their bribes for political influence. Nor are political slogans less subtle; "rum, Romanism, and ruin' is of the same mold as "corruption, communism, and Korea." Depressions were then called "panics" and "greenbackers" were inflationists. Socialism and federalization were in the budding stage. Yet there were those with wealth who were manifesting their great interest in the health and education of the citizens by large philanthropy: Mrs. John Rhea Barton, Johns Hopkins, Vanderbilt, Carnegie, and others; now it is largely the Federal Government to whom we look for aid and to whom we are beholden.

This particular season also was one of strong political campaigns. There is a remarkable similarity of forces and interference. The ambassador representing an empire that was and is one of our natural friends was instructed to state a preference for a particular candidate in the then approaching presidential election. The candidate was reelected and the ambassador was asked to leave. This year we find the leader of a strong foreign nation violently articulate in opposition to a party and a person in our present presidential election. Our present President was a military man; we have had 6 Presidents who had service in the Civil War

During the 1880's, the German institutions probably attained unparalleled heights. Scientific people in America and England sought an educational experience, brief though it be, in this provocative climate. There was conformity in scientific endeavor, at the same time tremendous rivalry. Bigotry and liberalism both prevailed, but there was a freedom of choice and interchange of students. In this decade the debates were humanities versus science; now it is specialization versus liberal education. It is noteworthy that a relatively large number of our founders sought additional training on the Continent.

Even now it is difficult to view in the broad scope of history the progress of medicine during this era. The records are fragmented by the beginning crystallization of specialty thinking and practice. It is easier to trace the growth of the specialties than it is to interpret accurately the reasons for actual inception of a specialty. A combination of discoveries and disciplines; histopathology, bacteriology, and physiology developed the concept that disease is seldom limited to a single organ, system, or discipline. The advances were widely scattered both geographically and scientifically. The positive evidence of progress was present and this progress carried the entire field forward in what is now recognized as orderly, though often delayed, fashion. The thinking is reflected in "the road to a clinic goes through the patho-

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logic museum and not through the shop of the apothecary" (Gull), and "we have always been prone, and not in universities alone or chiefly, to forget that the temple of education cannot be built without hands; the hand is the scientific instrument of the surgeon" (Albutt). Lawson Tait would have his son serve apprenticeship with carpenter or blacksmith before training in obstetrics and gynecology.

At one of the oldest and then as now one of the very best medical schools in an old university, the student who took two lecture courses for a term less than 4 months in length was entitled to his degree if he could prove that his total medical experience ran to 3 years and could pass a single examination. As late as 1870, the head of the school said that written examinations were out of the question because "a majority of the students cannot write well enough." President Eliot made changes which led to broader scholastic achievement for admission and a sustained curriculum in the School of Medicine.

A noted physician-investigator, the brother of a man who probably did most to improve medical education in this country, once described the first medical school he attended in 1887 as a "school in which the lecture was everything. Within the brief compass of four winter months, the whole medical lore was unfolded in discourses following one another in bewildering sequence . . . and, lest the wisdom imparted should exceed the students' power of retention, the lectures were repeated precisely during the second year at the end of which graduation with the degree of Doctor of Medicine was all but automatic."

As a personal note we find our own medical school, at that time offering only the preclinical years, made this announcement, "The Medical School offers daily lectures and requires students to dissect the human cadaver. Discipline is firm, but manly and self-respecting. There is no demerit system nor espionage. Students are treated as gentlemen." It is a bit whimsical that the president specifically used the term "gentlemen."

He probably realized his position in an humble vale that experiences a remarkable geographic and sociologic venous shurt whereby the state in which the first white live birth was recorded is bypassed, North and South, and even a blooded animal must name his sire.

During this decade we find a doctor in Mississippi writing that he "sent my white patients to Memphis and my colored ones to Vicksburg, but since none ever returned I quit sending them," while another perceptive doctor had established one of the early and best museums for pathologic specimens in Mobile and documented, before Simpson, the diagnosis and treatment of "coccydynia."

Apparently there were misgivings, then as now, concerning the feasibility and possibility of new schools and "remote" territory. In a letter to a friend regarding the possible departure of a brilliant young investigator to another location we find the sentence, "However bright the prospect is in Baltimore it is darkness compared with the career which is before him in a city such as New York." Ironically, some 50 years later the opposite of this philosophy was enunciated to a group of young men who departed Baltimore to participate in the founding of a new medical school 300 miles to the south; however, "Popsy" Welch was not one of the gloomy prophets. The distinguished British surgeon, Sir William MacEwan of Glasgow, had so little faith in American medicine that when he was offered an appointment by Johns Hopkins University he stipulated that he be allowed to bring his whole staff of nurses. Johns Hopkins withdrew the offer.

A speaker (quoting Herbert Spencer) described this period of change in medical thinking and practice as moving from the "homogenous to the heterogenous." It was evident in all medical practice and teaching.

One of the real investigators, teachers, and practitioners of the decade was reassuring: "Medicine is no worse off than the other professions. Theologians are tossed about on the storms created by their own imagining: the members of the bar are still fighting for personal advantage, while trying to maintain

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the higher laws; and statesmen are seeking self preservation as well as the interests of the countries they live in. So it is with medicine" (Skene).

In 1885 the task of organizing a program for the Ninth International Medical Congress was given to a doctor who was deservedly venerated, who was incapable of true injustice, but who was completely occupied with the selection and shaping of a new faculty in a new school, collecting and classifying books and specimens and doing impeccable recording. These facts plus the remarkable, and sincere, obliviousness to people and things beyond a local boundary, led to a select group of participants. The reaction was inflammatory and caused fairly widespread repercussion and correspondence here and abroad. The national medical association, then as now, endured abuse, some justified, some not, some from friends, some from those who had become disenchanted, and some from the provoked and hostile. Many thought that its progress was exasperatingly pedestrian, its thinking intransigent, and its motives often vindictive. A schism between the American Medical Association and certain state societies, notably New York, and some academic and national groups existed. The Medical Society of the State of New York in 1883 became a "no code" society after a revised code had led to a refusal by the American Medical Association to seat its delegates. This caused additional acrimony and led to a break in relations between the societies and to the development of a second state group, the New York State Medical Association. The man who did most to hold the State Society together and work toward an amicable agreement between all factions was our first secretary.

An American Surgical Society and an American Gynecological Society had been founded some 10 years previously; now an Association of American Physicians was being formed and preparation for a National Congress of American Physicians and Surgeons undertaken. In this age and in this climate the nebulous matrix of our Association was being formed.

At a meeting of the American Surgical Association, the subject of organization of American physicians and surgeons, the bringing together of the various special societies was thoroughly discussed. Later, sometime before the meeting in 1888, Dr. William H. Marsten, of Mobile, chairman of the Committee on Organization, informed Dr. Albert Vander Veer, of Albany, that the American Gynecological Society had declined to participate. He was greatly disappointed by their action and was anxious to have another society organized that would include subjects related to the specialty of obstetrics and gynecology. After further discussion at a meeting held in Buffalo on April 18, 1888, the American Association of Obstetricians and Gynecologists was formally organized. The secretary was directed to prepare the program and make official application for admission of the Association to the Congress of American Physicians and Surgeons and to meet with the Congress in Washington.

In the spring of 1888, Lawson Tait visited this country and his many professional friends and admirers. He was especially close to Albert Vander Veer, of Albany, Joe Price, of Philadelphia, and Potter, of Buffalo, and visited in their homes. It is believed that the attraction of his visit and his conversation with these men and others of like mind laid the foundation for this Association and gave the impetus leading to organization. Strong and abiding friendships made during the Civil War period, professional and geographic interests, academic ties and reciprocities, sheer ability, and attractive brilliance brought these men together. There is no evidence of truculence and there was a conspicuous absence of the fatuous and the pompous who are painfully familiar to all generations and to all times.

Undoubtedly, at this time there was pique. Among men who stand out in the profession there is always some disagreement, some inexact evaluation of others, even some resentment, and, among the sensitive, some hurt. Although there was duplicate memberships held in the older Society by some of the Association's early members, there was certainly

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a place and reason for the formation of our Association.

The correlated facts and circumstances were: in 1886 the American Gynecological Society passed a resolution favorable to the formation of the proposed Congress, but to "countenance no plan looking toward a surrender of its distinctive title or character or interfering with a full and complete management of its own affairs in every respect; amended so as to add that this Society will not favor a meeting of the Congress oftener than biennially; amended further, so as to add that this Society will oppose meeting of the Congress in the month of June." Later the proposition to become a part of the Congress was rejected. The Society decided to meet in New York in 1887 immediately after the International Congress in order that foreign visitors might also attend the session.

Many distinguished foreign guests did attend the International Congress, as did a number of the men who were the founders of the Association. At its New York session the American Gynecological Society planned to meet in Boston on the third Tuesday in September, 1888, but met instead in Washington. The reason as stated by the president was, "in March last a communication was addressed to me signed by well nigh every member of the Society asking that the place of meeting for the current year be changed from Boston to Washington City in order to participate in the joint meeting with the Congress." In Washington on Sept. 18, 1888, "the order of business was suspended and the resolution of last year declining to enter the Congress of American Physicians and Surgeons was rescinded and the motion to go into the Congress was unanimously passed." The Executive Committee of the American Congress held a special meeting (September 19) and unanimously resolved not to consider the application of any society who had not had two annual meetings. Notice was sent that if the Association would change its name so as to leave out "Gynecology" (either Obstetrics or Pelvic Surgery would be acceptable), it would be welcome as a member of the Congress. According to the Association's constitution such a motion would have to be delayed for one year because it necessitated a change in the document. A variety of events, some fortunate and some not, over several years thus transformed the tacit into an agreement, and an Association.

A year later (1889) the following telegrams were exchanged between the two societies: "The American Association of Obstetricians and Gynecologists, now in session, sends cordial greetings to its older sister and hopes its present meeting may contribute further to its already brilliant record," and the friendly acknowledgment: "The American Gynecological Society, now in session, acknowledges with pleasure the cordial greetings of the American Association of Obstetricians and Gynecologists and cordially reciprocates its kind sentiments."

In 1888 the presidential address given to the older gynecologic society stressed the wisdom of seeking the interest and participation of younger men by either "opening a wider door" or in "some delicate way" inviting application. This surely belies any evidence of unwillingness on the part of some members of the group toward other qualified workers who were not members. Rather the statement appears, "we must look to the younger and stronger men in the profession to replace, year by year, the weary and the worn in this work" (Battey).

And, in another association, we find this thinking, "we want an association in which there will be no medical politics and no medical ethics; an association in which no one will care who are the officers, and who are not; in which he will not ask from which part of the country a man came, but whether he has done good work, and will do more; whether he has something to say worth hearing and can say it" (Delafield, 1886).

Most of us now could associate topic to city in several papers presented at the Congress of American Physicians and Surgeons in 1888: "On the New Cesarean Section" (New York), "Vaginal Hysterectomy" (Chicago), "Palpation of the Uncter in the Female" (Baltimore), "Rupture of

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the Uterus" (Boston). A lone Southerner winte on "Pelvic Infection." Skene mentioned that during the last 75 years 6,000 books have been published on treating the diseases of women. In the past 8 years 804 books and 7,505 journal abstracts and pamphlets were added to the list, the majority of which were on gynecologic surgery. He urged a better balance and remarked that obstetric practice was more advanced and had done more that was good. He emphasized the wisdom and necessity of constant and varied study of all available publications. This also was the dominant theme of a younger Osler. Similar sentiment was put in more epigrammatic form by a contemporary humorist, later to become cynical, "the man who does not read good books has no advantage over the man who can't read them."

In our specialty at this time there was one national society, the section of the A. M. A. (though under a different designation) and 7 civic societies. The programs were uniformly excellent; competent workers had a podium and an audience. Their scientific opinions and attitudes toward special societies were freely stated.

At an early Association meeting there were 38 members present, 20 of whom held the rank of professor in schools as widely distributed as Keokuk, Fort Wayne, Toronto, and San Francisco. Other schools in the Midwest and East Coast were well represented. The recognition of capable doctors in such centers as Hartford, Newark, and other cities which had no medical schools is noteworthy. The roll recorded combined deans and professors of 4 medical schools, a lecturer in pathology, and a professor of physiology. It was noted that there were 4 professors of obstetrics, 2 professors of gynecology, 5 professors of obstetrics and gynecology, and 4 professors of surgery in attendance.

The ingle representative from Canada was highly pleased with his kind reception and friendly reciprocity and voiced the regret that, "the politicians of our two countries have placed a man at the border to make me open my grip-sack and expose my poverty."

In an early executive session the all too

familiar petty arguments concerning procedure were at a stalemate. The chairman asked a member from Alabama to adjudicate and received the following opinion, "a native of Suquatonchee, Mississippi, was asked the correct spelling of his town and replied, 'some spell it one way and some another, but according to my way of thinking there ain't no right way to spell it.'"

The evidence of altruism is demonstrated in a letter from one member to another in a distant city, who had agreed to sponsor a younger man, the simple request was, "feed him, water him, be kind to him."

A recurring thought is found in such sentences, "it is my hope that the Association will always endeavor to extend the most kindly courtesies to other general and special societies." It is remarkable how consistent have been the expressions and actions of every generation of the Association in attempting to carry out this compelling desire to help others. It was evident in the beginning by wise selection of honorary members, by allowing associate members so long as the need existed and by the often expressed reluctance to have any arbitrary limitation on membership except for interest, performance, and potential. Equally significant is the major role of this Association and its members in national, regional, state, and civic participation. Many have been aided in gaining a forum, becoming scientifically literate and individually articulate. If any deserve the sympathy of the obstetrician-autocrat who wrote, "alas for those who never sing but die with all their music in them," it is not because this Association has failed in offering a helping hand and receptive ears.

During the first two decades of this century we find the Association programs reflecting the alertness to change and advancement. The solid background of anatomy and pathology and the reward coincidental to asepsis were leading a natural course toward stronger efforts in maintaining normal physiology. There was more and more discussion of abdominal surgery and from 1900 on recurring requests to add the two words "abdominal surgeons" to the name

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of the Association. This is more understandable when we find such stalwarts as Crile, Deaver, Erdmann, and Murphy appearing as frequent and forceful essayists on the program. While under the tutelage of one of these leaders I well remember being given a reprint, together with a small blast and a large wink; the title, "The Decline of the Gynecologists and the Renaissance of the Abdominal Surgeon."

During this period the American College of Surgeons was organized and, after a predictable mixed reception in some sections, began to function effectively. This excellent organization was and is mutually beneficial to all the specialty societies. In 1918 there was a suggestion that a specialty or certifying board be established. This produced long discussion and it was the consensus of the members that the recently organized American College of Surgeons should and would satisfy this need by careful selection of its applicants for membership.

In 1919 the matter of altering the name of the Association so as to include the words "abdominal surgeons" was again presented. This required a delay of one year. There was a strong feeling in favor of the addition and the only obstacle was the matter of having articles dealing with surgery not in the abdomen or surgery performed on male patients published in the official journal. During this period the "Blue Journal" (The American Journal of Obstetrics and Diseases of Women and Children) was discontinued and THE AMERICAN JOURNAL OF OBSTETRICS AND Gynecology ("Gray Journal") launched. It was agreed that such articles deemed not suitable for the official journal be submitted to Surgery, Gynecology and Obstetrics. (In 1954 the words "Abdominal Surgeons" were dropped from the official name of the Association.)

In 1920 the first serious discussion was given to the suggestion that the Association invite an orator to the annual meeting. Apparently, the members felt that there were enough orators in the organization as constituted; actually, the matter of finances was the greatest deterring factor. During the

year the president of the Association and is council were leaders in establishing and promoting the section on "Diseases of Womer" in the American Medical Association.

In 1921 the controversial Sheppar l-Towner Bill (one of the early legislative acts that influenced maternal health) was under discussion. The Childrens Bureau was strongly in favor of this measure and believed that it presaged better maternal and infant care. The consensus of the Association was that it would be an apparent injustice against the Childrens Bureau to vote against it.

Motivated by a desire for healthy self analysis, in 1927 a committee was appointed to seek and select likely candidates in the United States and Canada. And, en route to the 1927 meeting, several members discussed a matter that had occupied their thoughts for some time and at the meeting Dr. Dannreuther offered a resolution that this society explore ways and means to form an American Board of Obstetrics and Gynecology. He was the first president. The second president also is a member of our Association. Further evidence of the desire for improvement and broader usefulness led to midyear meetings in medical centers. In 1929 the first Mid-Year Clinic was held in Columbus, Ohio. Also during this year a most important project was started. The Foundation of the American Association was organized and a charter granted in the State of Michigan. This was introduced in an unobtrusive manner by one of the most gentle of men. Kennedy's innate modesty was as sweetly evident as his complete competency; his love for his brother practitioner equaled his concern for his patient; the intangible, the things of the spirit, he was able to transform into the tangible; the present and the useful, into the betterment and enjoyment of his friends; all knew him as a friend.

The wisdom of establishing the Foundation was not accidental or without purpose. In 1927 funds were provided for the irst "Joseph Price Oration" by "a student and admirer of Joseph Price," and the Foundation, through Kennedy's example and benefactions, has continued to be the most grace-

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ful ornament in our society. The Joseph Price Oration is a lasting tribute to teacher and scholar.

n 1930 there was an interesting and somewhat alarming discussion on "birth control." Recent demographic studies indicated that there would be a pronounced, even critical, decrease in population by the year 1945. There had been a request that the Association and similar organizations lend their efforts to aid in discouraging willful population control and to encourage measures that would increase births. The ebb and flow of history is soon lost sight of. A population explosion is now predicted by demographers and is confronted by the paradox of the strong possibility of mass decimation by sudden or subtle radiologic phenomena. The same drug that seems to delay ovulation in the overly fertile, by rebound action can help the poorly fertile and maintain the pregnancy, albeit with the suggestion that some agents influence fetal anomalies. All this and "stress" too!

In the harassment incidental to learning, teaching, attending meetings, and preparing and reviewing material and in reflecting experience and knowledge into care of the patient, we sometimes temporarily doubt our sense of direction. But this we should remember, the improvement and high purpose in our specialty are largely due to a continuing educational process, to better communications and publications, and most important to the increase in the number of forums where precise presentations and critical review can furnish the refinement so necessary in processing a product for acceptance.

Our founders had a keen knowledge of ability, of devotion, and of the fact that

human beings are mortal. One who died 6 years after the organization had devoted a full life to a busy surgical practice in a rural area. "He prepared every bandage, disinfected every instrument, threaded every needle and remained with his patient until every danger was passed." He had performed 24 ovariotomies without a death; his wife died after an operation which he himself, of necessity, performed. His biographical sketch is concluded with this pathetic sentence: "His last days were darkened with sorrow from which we hesitate to lift the veil." This is not a cliché. This is not hackneved, unless the human heartbeat is hackneved. This is a natural expression of one who could have written otherwise but could not have written better.

All of us have a poignant sense of loss from the recent death of 8 of our members, 5 of whom were past presidents. We knew these men and loved them. They represent the composite of the things that are good in doctors, the things that are just, the things that are enduring. They sought, worked, and achieved, often in the certain knowledge that none or few would know or record what was done. The evidence comes but later in an increase in the total of knowledge, in helping those who in turn can help others do what is required of man, whether it be difficult and demanding or simply that of easing a tired heart. Their families and we their friends are sustained in the knowledge that "to His beloved He giveth sleep."

On the National Archives Building is the inscription, "The past is prologue," but a review of our heritage leads us in all sincerity to agreement with Plutarch, who wrote, "it is indeed desirable to be well descended, but the glory belongs to our ancestors."

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Jaundice in pregnancy

H. L. SHEEHAN, M.D.

Liverpool, England

JAUNDICE is not a very common complication of pregnancy. In the Liverpool maternity hospitals the incidence during the last 10 years has been only one case of jaundice in every two or three thousand deliveries. Furthermore, it is usually not a serious condition, and the great majority of the patients recover completely within 2 or 3 weeks. Nevertheless, it always gives rise to some concern, since there is always the possibility that the cause may be some severe damage to the liver and that death may occur from acute hepatic failure.

The present study is based on two groups of cases. The first group comprises 34 clinical cases of jaundice with full recovery. These cases provide a good deal of information about the course of the disease and the biochemical changes, but no information about the histologic appearances of the liver. The second group consists of an autopsy series of 50 patients who had definite jaundice during pregnancy. Some of the patients in this autopsy series died as a result of liver failure, while in others the jaundice was merely a minor aspect of a more serious disease. These autopsied cases were examined by me or by my assistants during the last 25 years; the clinical record are satisfactory and there are full pathologic and histologic details, but the biochemical studies were sometimes rather inadequate.

Clinical series

The clinical cases are subdivided in Table I according to the apparent cause. Most of these types will be considered later in relation to the autopsy series, and only the "hepatitis-hepatosis" group will be discussed here.

Hepatitis and hepatosis

The main group of patients had jaundice in which the clinical course followed a fairly regular pattern: there was a preicteric phase followed by jaundice which continued for 1 or 2 weeks and then gradually cleared up.

In 6 of the 26 cases the preicteric phase was similar to that in hepatitis in nonpregnant patients and was characterized by severe anorexia but little or no vomiting. These patients became jaundiced within 2 to 6 days after the onset of the anorexia. In the remaining 20 cases the preicteric phase began with a sudden onset of severe and intractable vomiting which continued throughout the phase. In a few cases there was also diarrhea. The jaundice developed in these patients sometimes within 2 to 5 days but more commonly after a period of 1 to 3 weeks.

Table II shows the mean figures of serum biochemistry in the cases, subdivided according to the period of gestation. It will be seen that the great majority of the cases occurred in the later weeks of pregnancy or very early in the puerperium. The serum bili-

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The Joseph Price Oration, presented at the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960.

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rubin was at ordinary jaundice levels. The thymol turbidity was above normal though not very high. There was usually only a moderate elevation of the alkaline phosphatase, but the figures were considerably raised in the patients who developed jaundice at about the time of delivery. (This estimation in England is made in King-Armstrong units, and the recorded figures have been divided by 3 in order to present them as Bodansky units.) A point which is not shown in Table II is that the cephalincholesterol flocculation test gave varied results in the patients who developed jaundice at 10 to 38 weeks' gestation but often gave a strong reaction in the patients who developed jaundice at about the time of delivery.

The etiology of the jaundice in this series of cases is uncertain and may be varied. There is evidence to suggest two distinctive types: (a) infective hepatitis and (b) a special type of "hepatosis" which is presumed not to be of viral origin.

Table I. Classification of "clinical series" (nonfatal cases)

	No. cases
Hepatitis or hepatosis	26
Obstetric acute yellow atrophy	1
Hemolytic jaundice	1
Cholelithiasis	3
Known toxins	3

Table II. Mean results of serum chemistry in clinical cases of hepatitis or hepatosis

Gestation at onset of jaundice	No. of cases	Bili- rubin (mg. per 100 ml.)	Thy- mol tur- bidity (units)	Alkaline phos- phatase (Bo- dansky units)
10 to 17 weeks	3	4.2	7.5	4.3
22 to 29 weeks	4	2.5	7.0	4.5
30 to 38 weeks	10	4.0	7.0	5.7
Delivery to 15 days post partum	9	6.4	7.5	16.5
Normal levels		0.1 to 0.6	1 to 4	1 to 4

Infective hepatitis. The simplest approach to the diagnosis of jaundice in pregnancy to presume that the condition is due to virus infection unless some other cause can be definitely established. This general at tude has been expressed or implied by vaious authors. 4, 5, 15, 16, 22, 23, 25, 46 It is proably significant that many of these workers have had personal experience of large epidemics of infective hepatitis in pregnancy. The main difficulty about the diagnosis of infective hepatitis is that there is as yet no method of identifying the virus in the laboratory. Transmission experiments to other human beings do provide definite evidence of the infectivity of the disease, but this is not a procedure which is to be encouraged. Thus, the diagnosis usually has to be based on indirect evidence, and often it is made only by a process of exclusion.

First, if the jaundice begins about 3 months after the taking of blood by syringe or needle, and particularly if other patients who subsequently develop jaundice have been attending the clinic at which this blood was taken, there are good grounds for assuming that the jaundice is due to infection transmitted in this way. Alternatively, if there is an epidemic of infective hepatitis in the region, any case of jaundice in pregnancy at that time is possibly one of the cases of the epidemic.

Second, the biochemical changes in infective hepatitis include relatively high figures for the various flocculation tests, as compared with only a moderate elevation of the alkaline phosphatase. If this pattern of biochemical changes is found in a patient without any obvious cause for the jaundice, it raises suspicions of infective hepatitis.

Third, as has been shown by Nixon and associates, ²⁹ Ingerslev and Teilum, ¹⁹ Caroli and co-workers, ⁸ and Bret and Sénère, ⁵ needle biopsy of the liver may give the histologic picture of severe hepatitis, although more commonly the histologic appearances are normal.

A review of the present clinical series with these three points in mind gives pre-

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sumptive evidence of a virus origin in only a few of the cases.

If syringe hepatitis were transmitted at the first one or two attendances at the antenatal clinic, it would be expected that the maximum incidence of the jaundice would be at about midpregnancy. In fact, about three quarters of the clinical series developed the jaundice later than 30 weeks' gestation. The difficulty in this argument is that many of the patients were subjected to a series of blood examinations throughout the pregnancy so that there were certainly opportunities for infection at various times throughout the course of gestation, and thus the jaundice might have developed at any time up to 3 months post partum. However, there are 6 patients in the present series who had only a single examination of blood, and the date of this is known. In 2 of these, the blood collection was 11 to 12 weeks before the onset of the jaundice, and the condition may reasonably be accepted as a syringe hepatitis. Interestingly enough, the preicteric phase in these 2 cases was rather long, 2 to 3 weeks. In the other 4 patients, the blood samples were obtained at 18 to 28 weeks before the onset of the symptoms, and, even allowing for the known variation of the incubation period, it cannot be inferred that the jaundice in these cases was due to the use of infected syringes or needles.

There were no serious outbreaks of epidemic jaundice in the town during the 10 years in which these cases occurred. Nevertheless, it is probable that there was some endemic infection in the population, as judged from the number of bottles of viruscontaining blood provided by donors to the local transfusion service.

The biochemical findings in these patients were compatible with, but not diagnostic of, infective hepatitis. The mean figures for the thymol turbidity tests were not as high as might have been expected.

Needle biopsy of the liver was not performed in any of the cases.

Thus, while it is certainly possible that many of these patients may have been suffering from infective hepatitis, the evidence presently available does not allow any definite conclusions on the matter.

Hepatosis. It is generally accepted that this type of jaundice results from the pregnancy itself and is quite distinct from infective hepatitis. It has been given various names: cholangeolitic hepatitis, cholostatic hepatosis, recurrent jaundice of pregnancy, or intrahepatic obstructive jaundice. The condition has been fully discussed by various recent authors.1, 8, 9, 17, 29, 41, 42, 43, 45

The descriptions in the literature are remarkably concordant. The onset is usually toward the end of pregnancy. There is a preicteric phase, which is often marked by generalized pruritus and by vomiting with epigastric pain, but there is no pyrexia. After a week or two the patient becomes jaundiced and bile appears in the urine. The jaundice usually continues throughout the remainder of the pregnancy, but clears up very soon after delivery. There is a tendency for the itching, and often also the jaundice, to recur at the same stage in all subsequent pregnancies. The thymol turbidity and other flocculation tests give low figures. The alkaline phosphatase is usually high, often at more than 10 Bodansky units, but in a few cases it remains at normal levels. The liver and spleen are not enlarged. Radiologic examination shows no gallstones, and there are no hematologic abnormalities. Needle biopsy of the liver does not show any lesions suggestive of infective hepatitis, but instead there are usually bile thrombi in the canaliculi, particularly near the center of the lobules,

This type of jaundice has a peculiar geographic distribution, in so far as can be judged from the literature. It is very common in Scandinavia, and has been reported occasionally in Germany and France. It is rare in America, and only one case seems to have been recorded in England.11 The frequency of reports in the last few years may indicate that the incidence is actually increasing, possibly because the causative factor is more common. On the other hand, the increase may be only apparent, and resulting from a greater awareness of the con-

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dition and a greater tendency to perform liver biopsies.

The etiology is obscure. The clinical, biochemical, and histologic findings indicate an obstructive jaundice apparently originating in the liver columns. There is nothing to suggest that this is due to virus infection. The tendency for the condition to occur late in the pregnancy, to subside rapidly after delivery, and to recur in successive pregnancies raises the possibility that it may be due to some biochemical or immunization reaction in relation to the pregnancy, and thus etiologically comparable to various other disturbances which occur in late pregnancy. On the other hand, the histologic appearances of hepatosis in pregnancy are indistinguishable from those of the jaundice produced by chlorpromazine, and the clinical course is very similar.2 Drugs of this series under a great variety of names are given quite commonly in pregnancy, either for the treatment of vomiting or for their tranquilizing effect. It is certainly possible that a proportion of the cases of hepatosis in pregnancy are due to such therapy; for the time being no valid estimate can be given of how high the proportion may actually be. In the present clinical series, chlorpromazine therapy was identified as the etiological factor in only one case, but its possible role does not seem to have been considered in many of the other cases. Since the completion of the series, 2 further cases of jaundice in pregnancy have been studied, and in each of them the jaundice began soon after the drugs of this group had been administered; no other cause for the condition could be found. It is difficult to establish a causal relationship, because patients in the preicteric phase of any hepatitis or hepatosis are commonly given these drugs to relieve the nausea and vomiting. Details of other drugs which may produce jaundice in nonobstetric patients will be found in the papers by Cachin and Levi7 and by Popper and Schaffner,32 but most of these drugs are probably not important causes of jaundice in pregnancy.

Scott³⁵ mentions the possible relation-

ship of hydrops fetalis to maternal jaundice, and reviews the previous literature. However, the great majority of women with jaundice in late pregnancy are delivered of live babies, and, if the jaundice is due to isommunization, some factor other than an ordinary rhesus incompatibility must be postulated. Furthermore, the maternal jaundice is not a hemolytic one.

In the present series of clinical cases there was one patient who had recurrent jaundice in her last 3 pregnancies. This is the only case in the series which fits the standard description completely. In addition there are 3 cases in which jaundice was preceded by pruritus and in which the biochemical findings would place them into this group, but there are no details about the preceding or succeeding pregnancies.

Thus, in the present clinical series there are about 3 cases that might be allocated tentatively to this hepatosis group. In the previous section it was concluded that 2 or 3 other cases had some evidence suggesting infective hepatitis. All the remainder of the series must be left without even this much explanation.

Autopsy series

The remaining cases of the clinical series may conveniently be considered with the autopsy series, since much of the information is applicable to both groups.

The analysis of the autopsy series has been extended to include not only the 50 cases of jaundice but also 21 cases of vomiting of such severity that the possibility of liver damage had to be considered and also 30 cases of related conditions. These cases are classified in Table III.

It will be noted that the autopsy series does not include any cases identified as infective hepatitis or as hepatosis. The absence of cases of infective hepatitis is probably because patients rarely die in the course of mild hepatitis and that the severe cases are represented in the autopsy series by the cases of true acute yellow atrophy. The absence of cases of hepatosis may again be because these patients nearly always re-

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7 able III. Autopsy series

	No. of	Weight of liver	(grams)
	cases	Range	Mean
Vomiting of late p	regnan	cy	
True acute			
yellow atrophy	2	700 to 780	740
Obstetric acute			
yellow atrophy	8	900 to 1,340	1,060
Idiopathic vomit-			
ing	16	1,280 to 2,600	1,720
Pyelonephritis or			
pyonephrosis	12	1,230 to 3,440	2,140
Hyperemesis	5	1,200 to 1,680	1,380
Cholelithiasis	14	1,490 to 2,740	1,890
Hemolytic jaundice	?		
Eclampsia	10	1,160 to 2,150	1,540
Transfusion	8	1,400 to 2,340	1,700
Abortion	1	_	
Chloroform	10	1,200 to 2,060	1,520
Sepsis	15	1,600 to 2,380	1,910

cover. Nevertheless it is peculiar that not a single example was found among obstetric patients who happened to die incidentally of obstetric complications; the histologic changes in the liver are striking and fairly characteristic and would not have been overlooked. It may possibly be relevant that most of the autopsy series was collected over 20 years ago and that hepatosis seems to have had its main incidence in the last 5 or 10 years.

Vomiting of late pregnancy

The cases of this general group have as the presenting symptom a sudden onset of severe vomiting which continues for varying periods up to about 3 weeks. This may mark the initial stage of severe liver damage or it may merely be an indication of some other disease. The series does not include the cases where there was merely a day or so of vomiting which was a symptom of severe pre-eclampsia and usually presaged impending convulsions.

In the early stage of vomiting of late pregnancy the diagnosis and prognosis may be very difficult. Most of the patients recover; some after a period of jaundice, as discussed above, but many without any jaundice at all. A certain number die. These fatal cases form a large group in the autopsy series,

but it must be emphasized that they do not represent the proportion in any ordinary clinical series.

Consideration may be given first to two conditions which begin as vomiting of late pregnancy but subsequently develop severe hepatic failure. They are clinically rather similar but show very different pathologic changes. These are "true acute yellow atrophy" and "obstetric acute yellow atrophy."

True acute yellow atrophy. True acute yellow atrophy is probably a fulminating version of infective hepatitis. The type of the virus, A or B, is of importance only in regard to the manner of infection and the incubation period, but certain strains of both types seem to be extremely virulent. The clinical course and the pathologic changes are the same in pregnant and in nonpregnant patients.

Clinically, the preicteric phase in the pregnant patients may be diagnosed originally as an ordinary vomiting of late pregnancy, but within a week there is jaundice and the urine contains bile. The characteristic cerebral symptoms then develop, and the patient dies in coma within a few days.

Biochemically, the flocculation tests give high figures and the alkaline phosphatase is much raised. The blood urea and uric acid remain at about normal levels. In the literature it is stated that the blood amino acids and the serum transaminase are high. The blood sugar is also recorded as very low,^{15, 21} but estimations were not done in either of the patients in the present series as they were being treated by intravenous glucose.

At autopsy the liver is very small. On section it has a mottled appearance of yellowish bile-stained areas and red congested areas. Histologically, there is necrosis of almost all of the liver cells, sometimes sparing a small cuff of parenchyma around the portal tracts. Some of the necrosed cells are small and others are about twice the normal size; this change must have occurred before the cells were killed. Some of the surviving cells have a coarse, fatty vacuolation.



Fig. 1. True acute yellow atrophy (low power).

In places many of the necrotic cells have disappeared and the sinuses in these areas are wide and filled with red corpuscles. All the portal tracts are heavily infiltrated by a mixture of lymphocytes and polymorphonuclear leukocytes, sometimes with some eosinophils among them, and these inflammatory cells spread out diffusely into the necrotic parenchyma.

The lesions in the 2 cases of the present series are quite characteristic of true acute yellow atrophy as seen in nonpregnant patients in general hospitals. They are similar to those described in pregnant women by Ezès and Bourdon¹⁵ in an excellent study with early autopsies and careful histology, and also to those in a personal collection of material from 30 autopsies on soldiers who

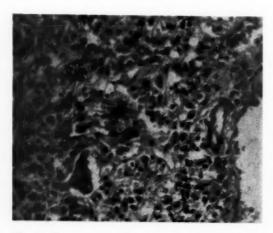


Fig. 2. True acute yellow atrophy (high power).

died of acute yellow atrophy during the last war. This histologic identity suggests that the cases in pregnancy are of viral origin.

Many of the records of acute yellow at rophy in pregnancy which are given in the earlier literature are unsatisfactory from the pathologic aspect. Commonly no pathologic details are given. When there is a histologic account, it is often clear that the picture is obscured by postmortem autolysis (in cases of jaundice the autopsy should be done within about an hour after death to avoid this autolysis). The older literature contains many accounts of so-called acute yellow atrophy which are without doubt merely examples of unrecognized delayed chloroform poisoning.

Obstetric acute yellow atrophy. In contrast to true acute yellow atrophy the most common finding at autopsy in the fatal cases of acute hepatic failure in the present series of pregnant patients is a condition in which the centrilobular part of the liver undergoes a particular type of fatty change without necrosis. This has been described under various names: obstetric acute yellow atrophy, acute fatty metamorphosis of the liver, or acute fatty liver of pregnancy. An account of 6 cases was given in an earlier paper. The present analysis deals with 8 fatal cases studied since that time.

The clinical disturbance begins at about 33 to 37 weeks and is in many ways similar to that of true acute yellow atrophy or of any other severe interference with hepatic function. The preicteric phase is characterized by severe and persistent vomiting with a rising pulse at 100 to 130 and weakness but no pyrexia. Sometimes this vomiting is preceded by a day or two of great thirst. After 1 to 3 weeks, slight jaundice develops, often associated with pain, which may be epigastric, retrosternal, or in the back at the level of the lower thoracic vertebrae. The urine contains acetone but no bile; the feces may be rather pale. Blood examination was made in 3 of the patients at this stage and showed moderate anemia with hemoglobin at 60 per cent and numerous normoblasts in the film. Within the next so re en in plant

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2 or 3 days the patient passes into a restless semicoma and is noisy and aggressive when roused. The jaundice becomes steadily deeper. The vomiting may become coffee-ground in type, and sometimes the patient complains of a sore throat. She goes into premature labor and is delivered of a baby which is usually stillborn (though in 2 cases of the present series a live baby was obtained by cesarean section). After delivery the coma becomes deeper, and some bile may appear in the urine on the last day of life. All the present patients died in coma at 12 to 60 hours post partum, usually with a terminal rise of temperature to 102 to 106° F.

In some of the cases in this series the biochemical records are not very detailed, but they are sufficiently consistent to provide a general outline. At the time that the jaundice first appears, the blood urea level is raised at around 70 to 100 mg. per 100 ml. This is presumably a result of the vomiting and dehydration. The plasma uric acid level is disproportionately raised and may be about 15 mg. per 100 ml. The plasma bilirubin level is in the region of 4 mg. Liver function tests show normal thymol turbidity at 1 to 2 units, but the alkaline phosphatase level is much raised at about 17 Bodansky units. Subsequently, the plasma bilirubin level gradually climbs to 7 or 8 mg.; the plasma uric acid level may rise even further to 20 mg., but the alkaline phosphatase may fall to 7 to 11 Bodansky units. The other figures remain relatively constant, and in particular the thymol turbidity continues normal. These biochemical changes contrast in certain ways with the findings in true acute yellow atrophy; for example, as regards the levels of uric acid and urea and the results of thymol turbidity tests.

Since obstetric acute yellow atrophy is nearly always an autopsy diagnosis, the morality appears to be extremely high. However, in the literature there are 2 cases where the patient recovered after the diagnosis had been established by needle biopsy. In one case in the present clinical series there was the characteristic clinical



Fig. 3. Obstetric acute yellow atrophy power).

and biochemical course of an obstetric acute yellow atrophy, although needle biopsy was not performed. The patient was treated with antibiotics and intravenous glucose; her condition began to improve about 3 days after delivery, and she had recovered completely by the fourteenth day. The first signs of improvement were a fall of the uric acid and the alkaline phosphatase levels, followed about 2 days later by a gradual fall of the plasma bilirubin level. Thus, the prognosis is not as hopeless as might be considered from the reports of autopsied cases.

At autopsy in the fatal cases there is often some ulceration of the mucosa at the lower end of the esophagus. As in any acidotic

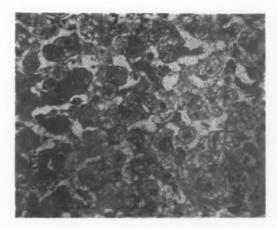


Fig. 4. Obstetric acute yellow atrophy (high power).

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patient, the proximal tubules of the kidney are fatty unless there has been treatment with intravenous glucose. The liver is small, but it is larger than in true acute yellow atrophy. On section it has a golden yellow color with pinpoint reddish brown dots indicating the site of the portal tracts. At an early autopsy it does not have the peculiar smell which is characteristic of normal fresh liver. The gall bladder contains a moderate amount of dark green bile, and the bile ducts are patent. These macroscopic appearances would suggest a true acute yellow atrophy in the early phase, but the histology is very different. The essential point is that there is no massive necrosis. The liver cells of the entire central and midzonal parts of the lobules are swollen and foamy as a result of a considerable amount of fat in very fine droplets throughout the cytoplasm; these appearances are quite unlike any ordinary fatty change in the liver. The nuclei are healthy and are large and leptochromatic. Rarely, a few small groups of unaffected liver cells may be seen in the centrilobular region; if so, they usually contain bile thrombi. The periportal liver cells remain quite normal and contain no fat or bile.

Scattered about in the central part of the lobule there are small areas containing a few lymphocytes or monocytes and a few medium-sized cells loaded with yellow pigment. Where these pigment cells and small monocytes are collected, the tissue often has a slightly empty appearance as if a few liver cells in the area have lysed and disappeared completely. Sometimes the small monocytes and the pigment cells accumulate under the endothelium of the central vein.

The portal tracts are usually normal. A few of them may have a light infiltration with lymphocytes and polymorphonuclear leukocytes, but this is never a striking feature.

One rather peculiar fact is that postmortem autolysis of the liver is quite slow, so that reasonably good histology can be obtained from delayed autopsies. This contrasts with the state in true acute yellow atrophy.

Various workers have discussed the problem of the small size of the liver. Presumably, though there is no massive necrosithere must be disappearance of a certain number of individual cells during the course of the illness. The small cells containing pigment would, on this view, be macrophages which have taken up some of the debris of lysed liver cells.

The etiology of obstetric acute yellow atrophy is not yet known. The histologic appearances do not suggest that this condition is the prenecrotic stage of a true acute yellow atrophy; in fulminating cases of true acute yellow atrophy with the patient dying after only 1 or 2 days of jaundice the liver shows the typical necrosis without any evidence of previous fatty change. There is no valid evidence that pregnancy can modify what would be true acute yellow atrophy to become obstetric acute yellow atrophy instead; many reports in the literature indicate quite clearly that true acute yellow atrophy does occur without any modification in pregnancy.

The fact that the condition occurs in late pregnancy and usually after the thirty-fifth week of gestation raises the same problems that were considered in discussing the clinical series of cases of jaundice. Many of the clinical and biochemical findings resemble those of cholostatic hepatosis, but the absence of bile in the urine is a discordant feature and the histologic appearances are quite different. Obstetric acute yellow atrophy has been known for over 25 years, so that modern drugs cannot be held responsible for it.

Good discussions of this condition have been published recently by Ober and Le Compte,³⁰ Moore,²⁸ Mason,²⁴ and Dyson,¹² Other accounts of probable cases have been given by Baens and Espinola,³ Whitacre and Fang,⁴⁴ Dill¹⁰ (Cases 1, 3, and 6), Barry and O'Dywer⁴ (Case 9), Piranoli,³¹ and Edwards.¹³

Idiopathic vomiting of late pregnancy. The 16 patients in this group developed -

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symptoms at about 33 to 37 weeks. Sometimes there was an initial stage of marked thirst for a day or so. Then severe vomiting began, and this continued for 2 or 3 weeks. During this time there was concern as to whether the condition was going to progress to serious liver damage. However, only 4 of the patients developed any jaundice; this was quite slight, with the plasma bilirubin level not more than 2 mg. and it occurred only in the last 2 or 3 days of life. The plasma uric acid rose to 10 to 13 mg., but the urea was only moderately elevated, reaching 40 to 80 mg. per 100 ml. The urine contained acetone but no bile.

No obvious cause for the vomiting could be found either clinically or at autopsy. However, 2 of the patients had severe macrocytic anemia with numerous normoblasts in the blood film. (The word "macrocytic" is used here in preference to "megaloblastic" because the bone marrow was not studied in these cases.) It is to be noted that a similar association of vomiting of late pregnancy with macrocytic anemia was seen in 2 cases of the hepatitis-hepatosis group in the clinical series of jaundice, and in 2 of the cases of obstetric acute yellow atrophy. The problem of whether this indicates some common etiological factor may be left over.

The cause of death did not appear to be related to any hepatic insufficiency. Three of the patients died of Wernicke's encephalopathy, which was precipitated in one of the cases by the intravenous administration of strongly hypertonic glucose solution. In 2 patients there was hemorrhagic infarction of the cortex of the suprarenals; this is a condition which may be due to fulminating septicemia, and there is some evidence that it may be produced by the intravenous administration of infected fluids. 40 The remaining 11 patients died of obstetric or other medical complications.

At autopsy the liver was of normal size. despite the history of 2 or 3 weeks of vomiting of all food. It showed no significant histologic lesions apart from some hemopoiesis in the patients with severe anemia.

Some of the patients who died late in the

puerperium had a moderate degree of ordinary fatty infiltration of the periportal region, but this appearance is seen in many patients who die in the puerperium without any history of vomiting and is probably only an indication of the mobilization of the body reserves. The important finding was a negative one: there was never anything to suggest even the early stage of an obstetric acute yellow atrophy. Nevertheless, it must remain an open question whether some of these cases of apparently idiopathic vomiting of late pregnancy may represent a forme fruste either of hepatosis or obstetric acute yellow atrophy and thus have the same basic causation. The present study has not been extended to cover the clinical cases of idiopathic vomiting which terminated in recovery, and thus no opinion can be expressed on the point.

Pyelonephritis and pyonephrosis. This group of cases of vomiting of late pregnancy is separated from the idiopathic group on the evidence at autopsy of a severe renal infection which probably gave rise to the vomiting. In 7 of the cases there was gross pyelonephritis affecting both kidneys and in 5 there was unilateral pyonephrosis.

Clinically the condition differed from idiopathic vomiting in beginning relatively early in the pregnancy, not uncommonly at 20 to 25 weeks. There were often the ordinary features of urinary tract infection. In addition a very mild jaundice occurred in 3 of the 12 patients in the last day or two of life. The cause of death in the present series was usually a combination of uremia and infection, although certain of the patients died from conditions similar to those in the idiopathic vomiting group.

At autopsy the liver was strikingly enlarged in most cases. Histologically it appeared normal and there was nothing to account for the large size of the organ.

As a control of the simple mechanical effect of obstruction of a ureter, 3 further autopsied cases have been reviewed in which there was gross unilateral hydronephrosis without infection. None of these patients had any vomiting or jaundice; their livers

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were of normal size (mean 1,660 grams) and showed no histologic abnormality.

Hyperemesis

Hyperemesis used to have the reputation of being an important cause of jaundice. This arose from the observations of 30 or 40 years ago, when many patients who died of hyperemesis were found at autopsy to have centrilobular necrosis of the liver, and this was considered to be a result of the hyperemesis. It is now known that the necrosis was due to the administration of chloroform for the surgical termination of the pregnancy, but patients with hyperemesis are still watched very carefully for the slightest trace of jaundice.27 An undue emphasis on disturbance of liver function in hyperemesis is to be deprecated, because it diverts attention from the important complications of the disease: the neurological disturbances and the dehydration uremia. It does, however, appear that jaundice can be an occasional complication of hyperemesis; Millar²⁶ observed it 5 times in 120 nonfatal cases of hyperemesis, and Thorling⁴³ recorded 6 cases. The cause of the jaundice may be extreme dehydration, and it sometimes responds to intravenous fluids.

In the present autopsy series there were 5 fatal cases of hyperemesis. Jaundice did not occur in any of them. At autopsy there were never any liver lesions but in all the cases the brain showed typical Wernicke's encephalopathy. The findings agree in general with those in a previous account of 19 fatal cases.³⁷

In the clinical series there were 2 cases of jaundice beginning at 10 and 13 weeks after only a week or two of vomiting. These patients may possibly have been suffering from true hyperemesis but were more probably cases of hepatitis.

Gallstones

It used to be generally accepted that pregnancy predisposes to gallstones, and it was sometimes inferred that jaundice due to gallstone obstruction should be more common in obstetric patients than in others.

Table IV. Incidence of gallstones at autopsy

	Fe		
Age group	Obstetric cases	Nonobstetric cases	Males
15-19	0/24	0/2	0/5
20-29	3/254	0/6	0/21
30-39	9/288	3/94	1/132
40-49	2/76	6/117	3/159
50-59	-	16/135	12/315
60+		44/335	45/563

In fact, Robertson and Dochat³⁴ showed in an excellent study that there is no relationship between pregnancy and gallstones. Large and associates²⁰ came to the same conclusion, but Horn¹⁸ was unable to exclude such a relationship absolutely.

The incidence of cholelithiasis varies from country to country, and, for this reason, an analysis has been made of the incidence of gallstones as found in the course of routine autopsies in Liverpool. This is shown in Table IV and confirms the findings of all previous studies: that the incidence increases steadily with age and that there is a higher incidence in women than in men. In the analysis, gallstones were found in 9 women aged 30 to 49 who died of causes unrelated to pregnancy. Three of these were nulliparas. These few figures do not indicate any special association of gallstones with pregnancy, since about 80 per cent of women in this age group in the general population have borne children.

The influence of pregnancy has been further investigated by analyzing the parity of the obstetric patients. If pregnancy plays a significant part in the causation of gallstones, it would be expected that there would be some relationship between the parity of these women and the incidence of cholelithiasis. In this analysis, it is necessary to take the age factor into account, because the obstetric patients dying before the age of 30 naturally include a higher proportion of primiparas than those dying after the age of 30. The data are subdivided in this way in Table V. The figures are too small to carry any mathematical significance, but

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tley do not show any obvious increase of incidence in relation to parity. Thus, as far as this evidence goes, it conforms with the findings of other workers that the higher incidence of gallstones in women is a function merely of their sex and age, and that pregnancy is not a causal factor.

Jaundice due to gallstones during pregnancy. In the autopsy series there were 14 women with gallstones, and 3 of them had characteristic obstructive jaundice due to impaction of gallstones in the common bile duct. In one of these women there had been jaundice twice during pregnancy but there were no symptoms at the delivery or subsequently. One developed jaundice shortly before delivery and this continued to death from another cause on the ninth day of the puerperium. The other patient had no symptoms until about 3 weeks after delivery, when she developed jaundice and also an empyema of the gall bladder which ruptured and caused fatal peritonitis. The liver in these cases tended to be large, and showed a few microscopic areas of inflammatory reaction presumably due to ascending infection.

Three of the patients in the clinical series had jaundice due to gallstones. The condition developed at about 30 weeks. The symptoms were pain in the right hypochondrium, tenderness over the gall bladder, and slight to moderate jaundice with some pruritus. The symptoms cleared up in the course of about a week, but 2 of the patients had a recurrence 2 or 3 weeks later. X-ray with radiopaque contrast medium showed gallstones. The condition seems to be clinically almost the same as in nonpregnant patients.

Table V. Relation of gallstones to parity in obstetric autopsies

Previous pregnancies	Age 16 to 29	Age 30 to 47
0	0/151	3/88
and 2	2/90	3/90
3 to 6	1/36	3/101
7 to 16	0/1	2/86

Hemolytic jaundice

Acute hemolytic jaundice is seen most commonly in 3 obstetric conditions: eclampsia, blood transfusion, and abortion.

Eclampsia. Jaundice was present in 10 out of 90 autopsied patients who had had eclamptic convulsions. From the histologic appearance of the liver in eclampsia it might quite reasonably be considered that the jaundice was a direct result of the liver lesions. However, there can be little doubt that the condition is really hemolytic jaundice. In the first few hours the plasma is red because of the presence of free hemoglobin and there is often a record of hemoglobinuria at this time. Furthermore, at autopsy on these eclamptic patients who have developed jaundice, the kidney always shows hemoglobin casts in the lower nephrons. Some hours after the original hemolysis the color of the plasma changes to orange, and the plasma bilirubin is then usually in the range of 4 to 8 mg. There may be clinically recognizable jaundice within 12 hours after the first convulsion. If the patient survives long enough, the jaundice usually fades within 3 or 4 days, and the plasma bilirubin reaches normal levels soon afterward.

The more difficult problem is to decide whether the hemolysis is entirely intravascular or whether some of it may be due to the breakdown of blood corpuscles in the eclamptic lesions in the liver. Clinical or pathologic evidence of hemolysis is rare in patients who have only periportal lesions, but it is found in about one third of the patients who have eclamptic necroses in the liver. However, the absence of hemolysis in the other two thirds raises the possibility that the necrosis and the hemolysis may both be indications of the severity of the "toxemic" process rather than that the necrosis gives rise directly to the hemolysis. This interpretation finds some support in the relative rarity of evidence of hemolysis in cases of abruptio placentae, although these patients not uncommonly have liver necroses similar to those seen in eclampsia.

If the hemolysis in eclampsia were due to the breakdown of red corpuscles in the liver

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necroses, it might be expected that other types of internal hemorrhage would also give rise to hemolysis and thus to jaundice. For this reason, an analysis has been made of 10 fatal cases of rupture of the uterus with gross hemorrhage into the retroperitoneal tissues or into the peritoneal cavity. Five of these patients died within 3 to 10 hours after the rupture, but the others survived for several days. In none of these cases was jaundice noted either clinically or at autopsy, and there were no hemoglobin casts in the kidneys. Biochemical examination of the plasma was not made in any of the cases, but from the clinical and pathologic evidence there can have been little, if any, increase of plasma bilirubin.

Incompatible transfusion. The hemolytic jaundice due to incompatible transfusion shows an identical pattern to that in nonobstetric patients. The hemolysis is obvious on examination of the plasma, and the jaundice is often recognizable within about 6 hours as a mild staining of the sclerae and the skin. The plasma bilirubin may reach 6 to 10 mg. (In this connection it should be pointed out that the Van den Bergh reaction must be interpreted critically; when there is a large amount of bilirubin in the plasma, a direct Van den Bergh reaction may be obtained in pure hemolytic jaundice.) Posttransfusion jaundice fades away within 4 or 5 days and the plasma bilirubin reaches normal in about a week. Any jaundice lasting significantly longer than this time is probably related to some liver damage rather than to transfusion. At autopsy in the 8 cases of this group the liver was usually normal, but sometimes it showed small focal necroses apparently resulting from the original shock for which the transfusion was given. The kidneys showed the standard hemoglobinuric lower nephron nephrosis.

Abortion. One patient in the autopsy series and one in the clinical series had jaundice following abortion. The fewness of the cases in the present material is due to extraneous factors and does not represent the incidence in other centers. The jaundice is hemolytic and there is usually an asso-

ciated hemoglobinuric lower nephron nephrosis. The etiological factor may possible be the injection of soap or detergents into the uterus and thus into the bloodstream, or a Bacillus welchii septicemia, or an idiosyncrasy to quinine or other abortefacient.

Other conditions. The literature contains occasional reports of congenital or acquired hemolytic jaundice as an incidental complication of pregnancy. These are reviewed by Rimbach and Beickert.³³ There is one case of this type in the present clinical series.

There were no cases of Weil's disease or of arseniuretted hydrogen poisoning in the material studied here.

Delayed chloroform poisoning

The autopsy series includes 10 cases of delayed chloroform poisoning which have been examined since an earlier paper on this subject.38 These patients had been given chloroform for delivery after a long labor. Some of them died too early to show gross symptoms but the others showed the standard clinical course. The jaundice is obvious on the second day after delivery and becomes rapidly worse. There is a progressive rise of the plasma uric acid and to a less extent of the urea. On the third day the patient becomes drowsy and delirious, and on the fourth or fifth day she is completely comatose with a rapidly rising temperature, and usually dies at this time. However, if she has been given intravenous glucose therapy immediately after the administration of the chloroform, the liver damage is not so severe and a fair percentage of patients can recover.39

At autopsy the liver is of normal size and has a yellow color with fine red dots corresponding to the lobules. Histologically there is a mid-zone necrosis which in severe cases spreads to involve the center of the lobule.

The use of chloroform in obstetrics has been almost discontinued and the present series of cases of delayed chloroform poisoning are thus mainly of historical interest. However, it is certainly possible that other anesthetics may be used in the future which

will have a similar toxic effect on the liver it given to patients whose metabolic condition is grossly disturbed, as for instance as a result of prolonged labor or vomiting. In a recent clinical case, an obstetric patient who had had much vomiting of late pregnancy was delivered under trichlorethylene anesthesia, and she developed jaundice about 2 days later, which lasted about a week. In a recent autopsy on a nonobstetric patient who had been given trichlorethylene, the liver showed a widespread centrilobular necrosis. These 2 cases are obviously quite insufficient to establish a causal relationship, but they raise a certain amount of suspicion.

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It is commonly believed that sepsis is a significant cause of jaundice. In order to assess this, an analysis has been made of about 150 autopsies on patients with various types of puerperal infection, including septic endometritis, necrosis of the entire myometrium, septicemia, pyemia, peritonitis, and pneumonia, but excluding those conditions which have been considered elsewhere in the present survey. The total number of cases is approximate, because many patients who die in the puerperium have had some pyrexia or a mild endometritis which would scarcely qualify as fatal puerperal sepsis.

Marked jaundice developed in one patient a few days before death; at autopsy she was found to have multiple pylephlebitic abscesses throughout the liver. In 7 of the other patients slight jaundice was noticed during the last day of life, often several days after delivery. The liver showed either a moderate fatty change of ordinary type or no lesions at all. The cause of this minor terminal jaundice is not very clear.

A further 7 patients in this group had microscopic necroses in the liver which had clearly developed only within the last day or two of life. None of these patients had recognizable jaundice.

Other causes of jaundice

Any of the other causes of jaundice which occur in nonpregnant patients may occur

in obstetric patients. In the autopsy series there was one case of lymphadenoma with extensive hepatic deposits causing jaundice. Though there were occasional cases of malignant disease they did not give rise to jaundice.

There were no examples of carcinoma of the pancreas or bile ducts, but Cattan and Cattan⁹ say that cases have been observed in pregnancy.

Cirrhosis of the liver is rare in pregnancy and does not usually give rise to jaundice, 6, 36 though a case associated with jaundice is recorded by Enrile and associates. 14

Summary

A review is given of the types of jaundice which occur in pregnancy. This is based on an analysis of 34 clinical cases with recovery and of 50 fatal cases with autopsy.

Vomiting of late pregnancy may be caused by (a) infective hepatitis or its virulent form, true acute yellow atrophy, (b) "cholostatic hepatosis," (c) the special type of acute hepatic failure without massive necrosis which is known as obstetric acute yellow atrophy or fatty metamorphosis of the liver in pregnancy, (d) pyonephrosis or pyelonephritis, or (e) some idiopathic factor.

Hyperemesis is not a cause of significant jaundice.

There is no etiological relationship of gallstones to pregnancy, but pregnant patients may develop obstructive jaundice due to gallstones.

Hemolytic jaundice occurs in about 10 per cent of patients who die after eclampsia. It is also seen after incompatible transfusion and some abortions, and as a result of ordinary medical causes.

Delayed chloroform poisoning is rare nowadays, but accounts for many of the cases of jaundice reported in the early literature.

Sepsis is a rare cause of jaundice, and this only as a mild terminal condition.

The other causes of jaundice in pregnancy are relatively unimportant.

I have to thank many obstetric colleagues both in Glasgow and in Liverpool for the clinical records of these cases, and Dr. Crawford and Dr. Stewart who carried out many of the pathologic investigations. The clinical cases analyzed in this paper are taken from the records of the Royal Maternity Hospital, Liverpool, and Mill Road Maternity Hospital, Liverpool, and from other hospitals in the region. Only a proportion of these patients have been seen by me personally I am indebted to Drs. C. H. Walsh, P. Malpas D. Prysor-Jones, A. G. Rickards, D. B. Mossman H. H. Francis, and others for their help in connection with these cases.

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Etiology of hypertension in toxemia of pregnancy

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While the presence of vasoconstriction in toxemia is universally accepted, the mechanisms responsible for this vasoconstriction are poorly understood. The recent finding of a vasopressor agent in the amniotic fluid and decidua of toxemic patients emphasizes the humoral aspect of this disease.¹

Hysterotonin has been demonstrated to be the end product of an enzyme, which is probably localized in the decidua, acting upon a protein in the amniotic fluid or blood. It is a heat-stabile polypeptide, not blocked by adrenergic blocking agents, and it possesses an oxytocic effect on the uterine muscle.

The finding of a pressor substance (hysterotonin) in the amniotic fluid and decidua in toxemic patients does not fully explain the maternal hypertension unless a pressor substance can be demonstrated in the maternal circulation. In this report evidence of pressor agents occurring in toxemic maternal plasma will be presented. These pressor agents may cause the pathophysiologic changes observed in this disease, namely, severe vasoconstriction.

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The increased frequency of toxemia in patients with multiple pregnancy, large babies diabetes, hydatid mole, and abruptio

placentae, and in conditions with preexisting vascular disease is well known. Frequently associated with these clinical entities are several mechanisms which may be contributing to one common factor observed in toxemia—uterine hypoxia. The uterine ischemia theory was first proposed by Young² more than 30 years ago. This hypothesis has been advanced by Page,³ Beker,⁴ Bastiaanse,⁵ Assali,⁶ and Browne.⁷ Two new, previously unrecorded observations will be reported in this study, substantiating hypoxia as being involved in the basic mechanisms underlying toxemia.

Methods and materials

1. Isolated aortic muscle strip. Spirally cut strips of rabbit aorta, as described by Furchgott and Bhadrakom,8 were used as a test organ for assay of dialyzed plasma and decidual and molar extracts. The spirally cut strips of rabbit thoracic aorta are well suited for both qualitative and quantitative investigations of the effect of drugs on arterial smooth muscle. The unstretched aortic strip was mounted in a muscle chamber having a 20 ml. capacity (Fig. 1). Krebs'9 bicarbonate solution, containing 0.2 per cent glucose, bathed the muscle strip. Through this solution 95 per cent oxygen and 5 per cent carbon dioxide were bubbled to maintain the pH of 7.4. The entire bath was maintained at 37° C. The aortic strip was attached to an isotonic lever with an eightfold amplification and counterweighted to exert 4 Gm. tension on the strip. A small vibrating motor was attached to the rod

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The Foundation Prize Thesis, presented at the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960.

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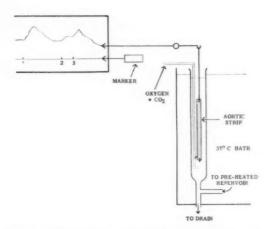


Fig. 1. Diagram of apparatus for detecting and recording constrictor substances.

holding the lever to promote relaxation of the muscle strip and to eliminate any friction of the stylus on the paper. The contractions were recorded on Waxer paper with a heated stylus attached to the lever.

2. Pithed nephrectomized cat. A cat, starved and nephrectomized for 2 days, was anesthetized with pentobarbital anesthesia and immediately pithed. After a lapse of 1 to 2 hours, the animal preparation was utilized for studying the vasopressor effects of the dialyzed plasma and molar and decidual extracts. A continuous blood pressure recording was obtained by a mercury manometer connected to a cannula inserted into the carotid artery. A cannula was placed in the external jugular vein for injection of the test solutions which were previously made isotonic.

3. Techniques of obtaining blood samples. The skin area over the femoral vein was prepared with soap and water and covered with thimerosal.* The skin and subcutaneous tissue were infiltrated with 1 per cent lidocaine.† A 13 gauge needle was inserted into the femoral vein and a specimen of blood withdrawn. A plastic catheter (1 mm. outside diameter) was then inserted through the needle for a distance of approx-

imately 15 cm. and a specimen of blood taken at this level (Fig. 2). The catheter was then advanced further cephalad until the level of the renal veins had been passed (approximately 28 cm.) and the third specimen of blood withdrawn. Heparinized syringes were used to prevent coagulation of the blood and all specimens were placed in ice until centrifuged. The plasma was dialyzed overnight in cold running tap water. The dialyzed plasma was made isotonic prior to testing.

4. Measurement of amniotic fluid pressure. A transabdominal uterine puncture was made in the paraumbilical area with an 18 gauge, 4 inch spinal needle, similar to the technique of Caldeyro and Alvarez. A spinal manometer was attached to the needle and amniotic fluid pressure recordings were

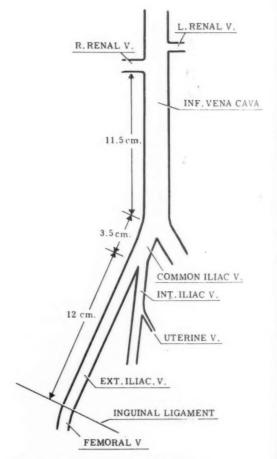


Fig. 2. Measurements of blood vessels.

^{*}Merthiolate, Eli Lilly and Company.

[†]Xylocaine, Astra Pharmaceutical Products, Inc.

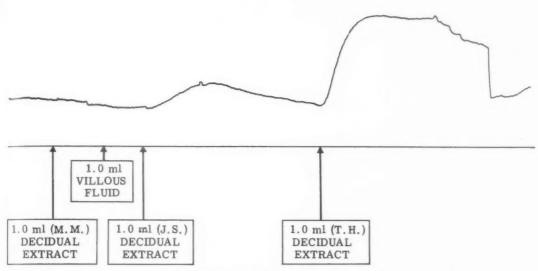


Fig. 3. Constrictor responses of villous fluid and decidual extracts from patients with hydatid mole and toxemia.

obtained. Amniotic fluid was withdrawn through the same needle.

5. Molar and decidual extracts. Decidual extracts were prepared similar to Helmer's technique for preparation of renin from the kidneys.12 This involves dilution of the fresh specimen with three parts of 0.9 per cent sodium chloride solution. This mixture is ground in a Waring Blendor until homogenized. The pH is adjusted to approximately 5.0 with glacial acetic acid. The extract is centrifuged and the supernatant fluid (residue discarded) is precipitated at 0.6 saturation with ammonium sulfate. This mixture is filtered by suction and the residue is dissolved in distilled water and dialyzed in a cellophane membrane with cold water for 18 to 24 hours.

Results

The response of the aortic muscle strip, upon addition of a normotensive molar decid-al extract (M. M.), is illustrated in Fig 3. The addition of this decidua to the muscle chamber did not result in muscular contraction. However, the addition of decidual extracts from patients with molar pregnancies with superimposed toxemia (J. S. and T. H.) resulted in contraction of the aortic muscle.

The patient (J. S.) whose last normal menstrual period was 4 months prior to her first appearance in clinic had a blood pressure of 142/90 mm. Hg.

The fundus was at the level of the umbilicus and moderately tense. She had bled intermittently since the last normal menstrual period. She spontaneously passed typical molar tissue, and a uterine curettage was performed.

T. H., an 18-year-old woman, had been followed in the clinic for a period of 2 months. The last normal menstrual period was 5 months prior to the original visit. At the twenty-second week of gestation, the blood pressure rose to 146/92 mm. Hg and the uterine fundus was at the level of the umbilicus. There was a moderately rapid enlargement of the uterus within the next 3 weeks. The blood pressure climbed steadily to a level of 160/100 mm. Hg and at this time the uterus was emptied.

This experiment demonstrates the presence of a constrictive substance in decidual extracts of patients with toxemia associated with molar pregnancy, and the absence of any constrictive substance in normotensive molar decidual extracts.

Fig. 4 demonstrates the inability of an adrenergic blocking agent, phentolamine

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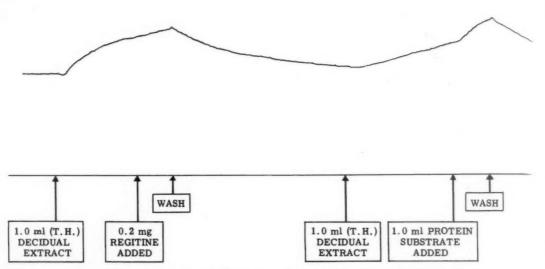


Fig. 4. Constrictor effect of decidual extracts from hydatid mole with superimposed toxemia.

methanesulfonate* to block the constrictive effect of a positive decidual extract (T. H.). The potentiation of the decidual extract with protein substrate can also be seen in this experiment. The pharmacologic properties of this decidual extract are identical to those of hysterotonin.¹

The isolated aortic muscle strip is utilized, also, to assay the vasoconstrictor effect of unknown plasmas. The constrictive response of the aortic muscle, upon the addition of ovarian vein plasma from a pre-eclamptic patient (P. J.), can be seen in Fig. 5. This patient had moderately severe pre-eclampsia, was in labor, and had cephalopelvic disproportion. The plasma was obtained at the time of cesarean section. It also demonstrates the inability of phentolamine methanesulfonate to diminish this constrictive response. A portion of this plasma was boiled for 10 minutes prior to testing in the muscle bath. A constrictive response occurred which was of the same magnitude as that of the unboiled plasma. This demonstrates the heat stability of this vasoconstrictor substance, which is highly significant in distinguishing from the vasoconstrictor substances formed from the renin-like system of renal origin.13

In the same experiment the constrictive effect of plasma from another toxemic patient (D. G.) is demonstrated. The addition of phentolamine methanesulfonate at the peak of the constriction diminished the response by approximately 30 per cent. A repeat dose of phentolamine methanesulfonate failed to lower the constriction further. Then, upon addition of 2.0 ml. of this same plasma, further constriction of the muscle strip resulted, in spite of the presence of phentolamine methansulfonate. A satisfactory explanation of this phenomenon is difficult. Dialysis of the plasma has removed substances of small molecular size, such as serotonin and catecholamines, prior to testing. The most logical explanation is that the substance is altered in the blood stream distal to its site of origin, causing it to react at the same receptor site as phentolamine methansulfonate on the muscle strip.

In Fig. 6 the presence of a constrictor substance in the arterial plasmas of 2 patients with toxemia of pregnancy is demonstrated. The absence of constriction following the addition of peripheral venous plasma is also demonstrated. The heat stability of this constrictor substance from Patient J. H. is noted.

The constrictor effect of plasma from a pregnant patient (M. M.) with essential

^{*}Regitine methanesulfonate, Ciba Pharmaceutical Products, Inc.

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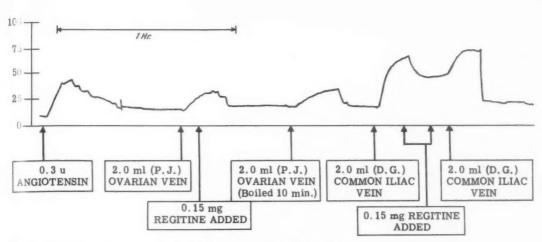


Fig. 5. Constrictor responses of rabbit aortic muscle to plasmas from patients with toxemia.

hypertension is illustrated in Fig. 7. This patient's blood pressure varied from 148/105 to 138/96 mm. Hg before and during the pregnancy. The slow acceleration of the constriction is indicative of incubation taking place directly in the muscle chamber. The potentiation of the plasma by protein substrate also is demonstrated. The salient point of this experiment is the complete in-

activation of the constrictive material by boiling. This is in direct contrast to the material observed in the ovarian veins, which is not destroyed by heat.

The constrictive effect of plasma in a patient with eclampsia (N. O.) is seen in Fig. 8. A marked constrictive effect is noted when plasma from the inferior vena cava of an eclamptic patient is added to the

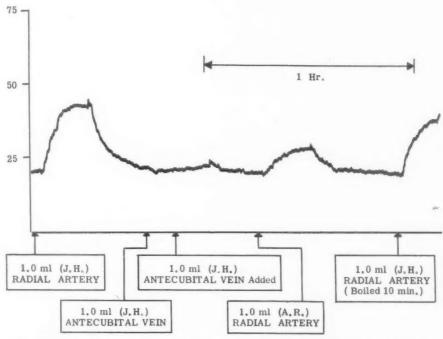


Fig. 6. Constrictor effects and heat stability of plasmas from patients with toxemia.

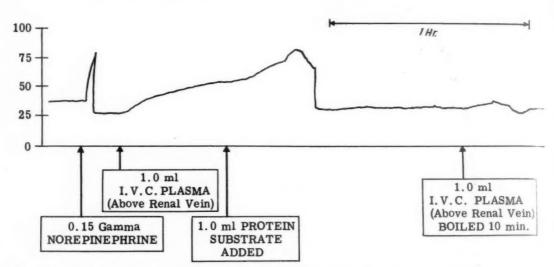


Fig. 7. Constrictor response of rabbit aortic muscle strip to plasma from a pregnant patient (M. A.) with essential hypertension.

muscle strip. Boiling the plasma for 10 minutes prior to testing reduces the constriction by 60 per cent.

The presence of a constrictor substance in the muscle chamber does not imply necessarily that this substance is vasopressor. Some vasodepressor substances also can constrict the isolated muscle strip. It is imperative, therefore, that all constrictor substances be tested in an intact animal for vasopressor effects. For this reason, the previously described cat preparation is utilized.

The vasopressor effect of a few of the previously determined constrictor substances is shown in Figs. 9 and 10. The injection of a decidual extract from a molar pregnancy with superimposed toxemia (T. H.) resulted in a 50 mm. Hg increase in blood pressure. This is compared to the blood pressure response resulting from a standard dose of angiotensin.

The blood pressure response of equal doses of plasma from different locations is shown in Fig. 10. Upon the injection of 4 ml. of plasma from the femoral artery resulted in a rise of 24 mm. Hg. Four ml. of plasma from the ovarian vein resulted in a 30 mm. Hg rise in blood pressure. An equal dose of plasma from the femoral vein resulted in a 15 mm. Hg rise in the cat's blood pressure.

All constrictor substances in this study have revealed similar vasopressor effects.

In order to determine the effects of decreasing the amniotic fluid pressure in toxemic patients, varying amounts of amniotic fluid were withdrawn by transabdominal uterine puncture. The maternal blood pressure was monitored before, during, and after the withdrawal of amniotic fluid (Fig. 11). I. A. was a 25-year-old obese primipara who was admitted to the hospital at term for control of toxemia. The blood pressure was 160/100 mm. Hg with 3-plus albuminuria. The uterine tonus was elevated, with an amniotic fluid pressure of 20 mm. Hg. Upon removal of 200 ml. of amniotic fluid, the maternal blood pressure rapidly decreased to 118/80 mm. Hg and remained in a normotensive range for one hour. After removal of the amniotic fluid, the uterine tonus had decreased to a normal range [13] mm. Hg).

In Fig. 12 the effects of withdrawal of amniotic fluid in an eclamptic patient (N. D.) are shown. This 19-year-old gravida i was admitted to the hospital, having convulsions, with a tense uterus but no clinically palpable contractions. The amniotic fluid pressure was 26 mm. Hg and, after removal of 325 ml. of fluid, the intrauterine pressure dropped to a normal level of 8 mm. Hg.

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Fig. 8

Before the amniotic tap, the blood pressure was 180/120 mm. Hg and fell to 134/78 mm. Hg within 20 minutes. After a period of approximately 2 hours, the blood pressure gradually rose to 180/104 mm. Hg. Thirty hours later, the blood pressure was 230/120 mm. Hg and a second amniotic tap, with removal of 80 ml. of fluid, resulted in a decrease in the maternal blood pressure (from 230/138 to 160/100 mm. Hg).

It may be concluded from these results that a decrease of an elevated intrauterine pressure results in a marked decrease of an elevated blood pressure in patients with toxemia. This effect has not been observed in pregnant patients with essential hypertension.

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The demonstration of a vasopressor substance in the decidua of molar pregnancies with superimposed toxemia fulfills a major etiological criteria for this disease. In a previous study, the authors were able to demonstrate a pressor agent, hysterotonin, in the decidua and amniotic fluid of toxemic patients. The inability to demonstrate any vasoconstrictor activity in normal or molar placentas tends to eliminate this organ as a source of the pressor agent.

The occurrence of postpartum toxemia lends further support to the theory of the decidual tissue being involved in the production of hypertension in toxemia. The time of occurrence of postpartum toxemia seems to be related to the viability of the decidua. In a current study by the authors, 14 removing the decidua by immediate postpartum uterine curettage had a beneficial effect on lowering the maternal blood pressure in toxemia.

In order to explain the hypertension in toxemia, a vasopressor substance must be demonstrated, not only in the uterus, but also in the maternal circulation. In pre-eclampsia a pressor substance, having many of the same characteristics as hysterotonin, has been found in higher concentrations in the plasma obtained from the ovarian and common iliac veins than in plasma collected from more distant locations from the uterus. This indicates these pressor substances originate from within the uterus.

One of the most outstanding characteristics of the pressor substance in the plasma from patients with pre-eclampsia is that of heat stability, which delineates this substance from that described in renal hypertension.

In patients with essential hypertension without superimposed pre-eclampsia, the constrictor effect of the plasma is destroyed by boiling. This characteristic (heat lability) of the plasma and the inability to demonstrate hysterotonin in the decidua differentiates these patients from the patients with essential hypertension with superimposed toxemia.

Pressor substances have been demon-

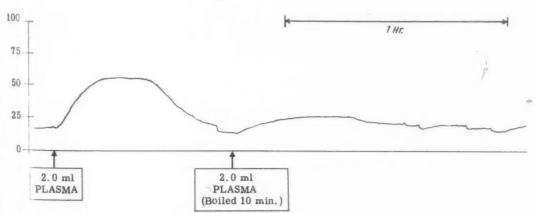


Fig. 8. Aortic muscle responses to plasma from inferior vena cava above renal vein (eclamptic patient).

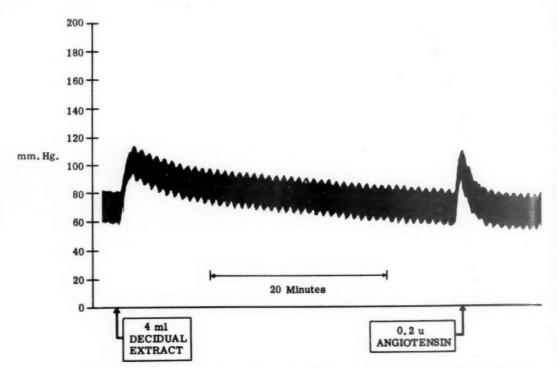


Fig. 9. Pressor response from a patient with toxemia associated with molar pregnancy.

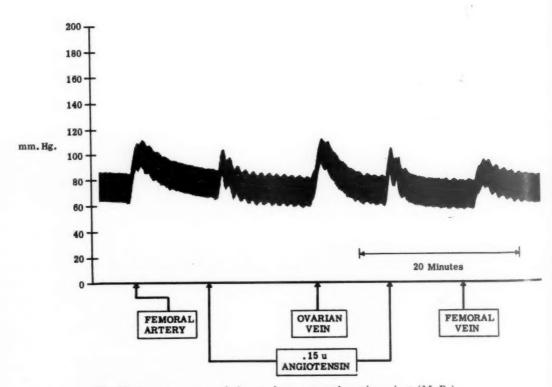


Fig. 10. Pressor response of plasmas from a pre-eclamptic patient (M. R.).

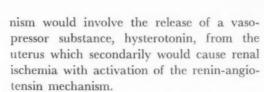
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Direct evidence that decidual hypoxia precedes the elaboration of the pressor substance, hysterotonin, is difficult to demonstrate. Measurements of uterine blood flow fail to distinguish primary from secondary uterine hypoxia. Unpublished data by the authors,15 from a study of 94 normal and abnormal pregnancies in the last trimester. reveal markedly decreased oxygen saturation levels of the intervillous blood in toxemia. Several severe cases of toxemia have had oxygen saturation levels 30 per cent to 35 per cent lower than normal patients. These lowered oxygen saturation levels in the intervillous space do not pinpoint hypoxia as being primary or secondary factors, however.

One of the most direct pieces of evidence of the role of hypoxia in the production of hysterotonin is the significant fall in maternal arterial pressure upon the reduction of an increased amniotic fluid pressure. This phenomenon probably is due to cessation of release of hysterotonin from the uterus because of improved uterine oxygenation. The

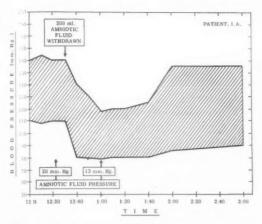


Fig. 11. Blood pressure response on withdrawal of amniotic fluid in toxemia.

strated also in the plasma from patients with eclampsia. These pressor substances are similar to hysterotonin, but they are partially inactivated by heat. This partial heat lability pattern is similar to those reported by Helmer¹³ in nonpregnant patients with renal hypertension. Does this indicate that the renin-angiotensin mechanism is involved also in eclampsia? Since hysterotonin has been demonstrated in the decidua in eclampsia, it would appear that at least two vasopressor agents are involved in eclampsia. A logical explanation of this dual mecha-

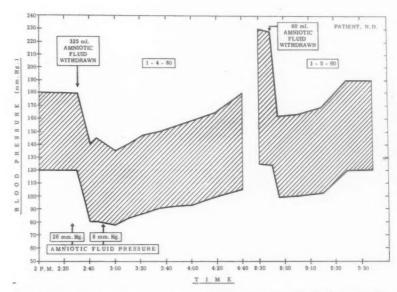


Fig. 12. Blood pressure response on withdrawal of amniotic fluid in toxemia.

uterine blood flow is inversely related to the myometrial tone—increased myometrial tone results in a decreased uterine blood flow. Conversely, the diminished amniotic fluid pressure secondary to amniocentisis results in a relative uterine hyperemia with a fall in the maternal blood pressure. Increased intrauterine pressure is not universal in toxemia, however, and the uterine ischemia of these cases is probably due to extrauterine factors which affect uterine oxygenation.

The authors believe that hypoxia is the primary alteration in initiating the formation of hysterotonin in the decidua in toxemia of pregnancy. With the release of this pressor substance into the maternal circulation, the pathophysiologic change, vasoconstriction, is produced.

Summary

1. A pressor substance (hysterotonin) has been demonstrated in the decidua obtained from patients with hydatid mole with superimposed toxemia. No hysterotonin has been observed in decidua from normotensive patients with hydatid mole.

2. Vasopressor substances have been demonstrated in the maternal plasma of patients with toxemia. In eclampsia there seem to be two pressor substances, one is heat-stabile and has many of the same pharmacologic properties of hysterotonin, and the other is heat-labile and has many characteristics of the renin-like pressor system. To date, only one pressor substance (heat-stabile) has been demonstrated in pre-eclampsia.

3. The reduction of an elevated intrauterine pressure by withdrawal of amniotic fluid in toxemic individuals results in a marked fall in the maternal blood pressure.

4. Hypoxia is the underlying common denominator responsible for the release of hysterotonin in the uterus in toxemia. The hypertension of toxemia of pregnancy is due to these pressor substances in the maternal circulation.

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Incidence of anomalous development following maternal rubella

Effect of clinical infection or exposure and treatment with gamma globulin

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THE recognition that a viral infection could be a causative factor in congenital defects was forcibly brought to the attention of the medical profession by Gregg.1 By a retrospective study, he was able to show a high incidence of congenital cataracts in children whose mothers (87 per cent) recalled having had rubella in the early months of pregnancy. This report established an entirely new concept concerning nonhereditary congenital anomalies and stimulated others2-9 using the same methodology to search for the teratogenic effects of the rubella virus. Some of these investigators reported the occurrence of fetal malformation following maternal rubella to be 70 to 100 per cent, and on the basis of this high incidence therapeutic abortion was advocated by many.^{3, 6, 10, 11} The data from a retrospective study are subject to criticism in so far as providing a satisfactory estimate of incidence, but these workers established the type of anomaly most likely to result when the mother had rubella in the first trimester of pregnancy. It has become known as the rubella syndrome and consists of congenital cataracts, heart disease, deafness, microcephaly, and mental retardation.

Lundstrom12, 13 and Greenberg and his coworkers14 were among the first to report the results of prospective studies. Observations were instituted during pregnancy with the occurrence of rubella, and the fetal outcome was assessed. These studies indicated a 10 to 20 per cent risk of congenital anomalies, the majority of the infants being normal. Because all fetal and obstetrical abnormalities were included in Lundstrom's reported incidence of anomalies, some have thought that incidence too high. The present study is an attempt to evaluate, on a prospective basis, the effects of maternal rubella on the fetus. Although such an investigation presents certain problems in provision for absolute control, siblings of study infants were included as a comparison group for

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Aided by a grant from The National Foundation.

Presented at the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960.

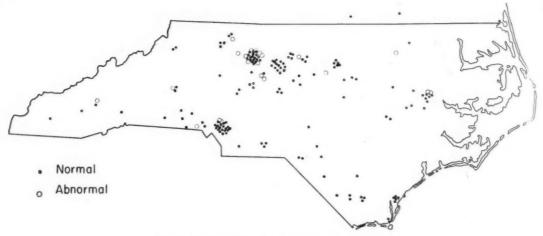


Fig. 1. Geographic distribution of study cases.

"control" purposes. These observations may be of interest because of the paucity of available data concerning the hazard of maternal rubella for the fetus during successive weeks of gestation or the significance of exposure to rubella without overt disease. In 1958 a severe epidemic of rubella occurred in North Carolina and provided an opportunity to carry out this prospective study (Fig. 1).

Method

The criteria for the present study include the following:

- 1. Selection of cases was made at the time of rubella infection or exposure.
- Infection or exposure in all stages of pregnancy was included.
- 3. The diagnosis of rubella was made by a physician when possible. Those women not seen by a physician at the time of rubella infection were eliminated from the study unless their description of the illness was typical.
- 4. Each child was examined by a trained medical investigator.
- A comparison group for the purpose of control was obtained by examination of the siblings.

All practicing physicians in North Carolina were mailed an inquiry with forms for reporting patients who had rubella during pregnancy in the recent epidemic or who had been exposed and treated prophylactically with gamma globulin. Physicians provided the dates of the last menstrual period, of infection, or of exposure and treatment with gamma globulin. Each infant in question was examined by a trained medical investigator (H. B. G.). Other pertinent data relating to type of delivery, socioeconomic conditions, and complications of pregnancy were also accumulated. All doubtful and recognizable defects were confirmed or disproved by consultation with certified specialists. A comparison group was obtained for analysis of hereditary and environmental factors through the examination of living siblings and records of those who had died.

Material

The initial survey yielded reports from 85 physicians concerning 223 pregnant women who had been infected by or exposed to rubella. The field investigator visited these physicians to review their records, document the diagnosis of rubella, and gather all pertinent factors related to the pregnancy.

Nineteen pregnancies terminated in abortion in the first trimester, 11 spontaneous and 8 therapeutic. Twelve patients delivered prior to the beginning of the study and 16 who could not be found or failed to quelify for a prospective study were eliminated. One patient with an apparently normal child

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Diagnosis in rubella group. A physician made the diagnosis of rubella for 36 patients. For 48 patients, the physician had made a clinical note that the patient had rubella on a basis of verbal report of exposure and the presence of typical symptoms. The investigator obtained a detailed description of the illness from each group for confirmation. In view of the presence of a severe epidemic and an accurate description of the clinical signs and symptoms by the patient, we believe the documentation of the rubella infection is satisfactory.

Gamma globulin. Eighty-three pregnant women exposed to rubella during the epidemic received gamma globulin and did not develop symptoms of rubella. The investigator confirmed the exposure and the date and dosage of gamma globulin administered. The dosage ranged from 0.35 c.c. to 24 c.c.; however, the majority of patients received standard dosage (0.1 c.c. per pound of body weight) from within a few hours to more than 7 days after exposure. Fifteen were treated 7 days or more after exposure.

Eight patients who received gamma globulin subsequently developed typical or atypical symptoms and signs of rubella. Three received 2 c.c. of gamma globulin or less; 5 received standard dosage. Two of the patients had been re-exposed to infection, one of these 5 and the other 7 weeks after treatment. These 8 patients are considered as a separate group since the situation is modified.

Time of infection in pregnancy. The difficulty of establishing the exact duration of pregnancy is known. For the present study the date of the first day of the last menstrual period was obtained. This date was recorded for each patient in the preliminary survey to find the study groups. It was confirmed from the physician's record and by the interview with the patient. The exact date of the rubella infection was also subject to these three sources of confirmation. The gestational age at time of rubella infection was determined in weeks following the first day of the last menstrual period, disregarding the physiologic interval to fertilization. The date of delivery and birth weight of the fetus were correlated with the previously determined duration of pregnancy for evidence of discrepancy. The distribution of mothers in the three series is shown by trimester of infection or exposure and treatment with gamma globulin in Table I.

Other factors associated with congenital anomalies. The data include a record of all major factors associated with an increase in the incidence of fetal anomalies. Table II shows the incidence of anomalies among

Table I. Distribution of mothers by duration of pregnancy at time of infection or exposure and treatment with gamma globulin

		Series	
Duration of pregnancy		ed with gamma globulin	
(weeks)	I—Rubella	II-No subsequent symptoms	III-Subsequent rubella symptoms
1-13	39	60	3
14-26	30	19	3
27 or more	15	4	2
Total	84	83	8

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Table II. Major factors possibly associated with fetal abnormalities*

		Rubella			sed and tree gamma glo	
		Anomalous		Anomalous		
Characteristic	Total	No.	. %	Total	No.	%
Mother's age (years)						
Under 20	19	2	10.5	4	2	50.6
20-29	53	11	20.7	57	5	8.8
30 and over	13	1	7.7		0	-
Total	85	14		91	7	
Birth interval (multipara)						
Under 1 year	6	0	-	2	1	50.0
1 and 2 years	30	5	16.7	27	2	7.
3 years or more	17	4	23.5	40		-
Total	53	9		69	3	
Number of previous pregnancies						
None	28	4	14.3	11	1	9.
One or more	57	10	17.5	80	6	7.
Total	85	14		91	7	
Economic status						
Low	52	9	17.3	23	1	4.
Middle-upper	31	4	12.9	68	5	7.
Total	83	13		91	6	
History of hereditary disease (family	ly)					
None	56	10	17.9	63	6	9.
Some (positive)	29	4	13.8	29	1	3.
Total	85	14		92	7	
Prenatal course						
Normal	70	11	15.7	66	5	7.
Abnormal	15	3	20.0	26	2	7.
Total	85	14		92	7	
Type of delivery						
Spontaneous	76	13	17.1	84	6	7.
Operative	9	1	11.1	- 8	1	12.
Total	85	14		92	- 7	
Birth weight (grams)						
Under 2,501	9	1	11.1	0	-	-
2,501 or more	76	13	17.1	91	_ 7	7
Total	85	14		91	7	
Neonatal difficulty						
Normal	79	11	13.9	90	6	6
Other	6	3	50.0	2	_1_	50
Total	85	14		92	7	

*Cases in which the characteristic is unknown are excluded; therefore, the sum may not be equal to the total. †The 8 patients who were treated and subsequently developed rubella-like symptoms are included in this group.

Table III. Gross incidence of abnormalities of rubella group by trimester*

Trimester	Gestational week of infection	Total cases .	No. with abnormal outcome	Percentage anomalies
First	1- 4	6	3	50.0
	5- 8	14	4	28.6
	9-13	19	5	26.3
Second	14-26	31	1	3.2
Third	27-40	15	1	6.7
Total		85	14	

The normal approximation for the binomial distribution was used to test the difference between the percentage abnormalities in the first trimester as compared with that of the siblings of this group. The difference was significant at the 0.05 level.

Table IV. Congenital anomalies in rubella group

Case	Last menstrual period	Gesta- tional week at delivery	Gesta- tional week of rubella	Birth weight (grams)	Age at final examination (months)	Anomaly
0362	4/ 2/58	38	3	3,119	18	Patent ductus arteriosus and mild tetralogy of Fal- lot or intraventricular septal defect, unilateral cataract and microphthalmia, retinal degenera- tion, right mental retardation, microcephaly
0352	3/18/58	41	4	3,399	18	Congenital heart disease (aortic stenosis or intra- atrial septal defect), bilateral cataracts, mi- crophthalmia microcephaly, mental retardation syndactylism, hypospadias
0312	4/ 2/58	38	4	2,523	18	Congenital heart disease (intraventricular septal defect or mild tetralogy of Fallot), severe bilateral nerve deafness, microcephaly
0262	2/13/58	38	6	2,948	19	Congenital heart disease (pulmonary stenosis)
0282	1/18/58	40	6	3,399	21	Patent ductus arteriosus, microcephaly, mental retardation(?), petit mal epilepsy
0292	2/ 2/58	42	8	2,523	21	Congenital heart disease (intra-atrial septal defect); alternate diagnosis: intraventricular septal defect or patent ductus arteriosus
0272	2/16/58	42	8	2,325	20	Moderately severe bilateral hearing loss, microcephaly, mental retardation, bilateral retinal pigmentation
0302	3/29/58	39	9	2,948	17	Polydactyly (extra left toe and metatarsal)
037 /	2/ 1/58	41	9	2,523	18	Mental retardation(?), cryptorchidism
038_	2/12/58	40	10	2,807	20	Congenital heart disease (intraventricular septal defect) bilateral hearing loss(?), mental retardation, retinal pigmentation, bilateral
033_	2/14/58	40	11	2.552	18	Exstrophy of bladder, epispadias, hyperphalangism
0322	12/10/57	40	13	-3,005	22	Cerebral palsy (spastic quadriplegia), mental retardation
0682	1/13/58	41	14	3,441	20	Cavernous hemangioma, left side of face
0742	10/ 6/57	36	27	3,567	24	Inguinal hernia

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children of the rubella pregnancies and the combined gamma globulin groups of pregnancies according to some potential causal factors. None of the differences between factors within either group in Table II is statistically significant. Although complications of the prenatal period are grouped in the table, the records contain specific information about drugs, hormones, diagnostic and therapeutic radiation, antenatal bleeding, and other maternal infections. These and other specific complications considered to affect fetal development have been

analyzed individually and collectively in relation to the outcome.

Study children. The study children are divided into four major groups: I, 85 children born following rubella infection in pregnancy; II, 84 children born following exposure of the mother to rubella and treatment with gamma globulin without developing symptoms; III, 8 children of mothers who developed rubella after gamma globulin treatment; and IV, 231 siblings of the study groups. Because of differences in the characteristics of mothers in the study groups,

Table V. Summary: first trimester rubella group

Case	Last menstrual period	Gestational week at delivery	Gestational week of rubella	Birth weight (grams)	Age at final examination (months)	Result
0042	3/29/58*	40	1*	3,476	17	Normal
0162	3/26/58	40	2	3,062	19	Normal
0242	2/12/58	41	3	2,559	20	Normal
0362	4/ 2/58	38	3	3,119	18	Abnorma
0352	3/18/58	41	4	3,399	18	Abnorma
0312	4/ 2/58	38	4	2,523	18	Abnorma
0022	2/13/58	41	5	3,609	20	Normal
0142	4/27/58	40	5	3,301	17	Normal
0262	2/13/58	38	6	2,948	19	Abnorma
0282	1/18/58	40	6	3,399	21	Abnorma
0032	3/ 1/58	41	6	4,029	18	Normal
0132	3/27/58	38	6	3,539	18	Normal
0122	2/25/58	36	6	3,047	21	Normal
0202	2/10/58	39	7	3,259	19	Normal
0092	3/13/58	38	7	3,033	19	Normal
0052	2/10/58	40	7	3,581	18	Normal
0292	2/ 2/58	42	8	2,523	21	Abnorma
0272	2/16/58	42	8	2,325	20	Abnorma
0102	1/30/58	39	8	3,033	20	Normal
0342	5/ 1/58	38	8	2,722	17	Normal
0152	2/28/58	40	9	2,637	18	Normal
0222	3/ 1/58	39	9	3,371	20	Normal
0302	3/29/58	39	9	2,948	17	Abnorma
0372	2/ 1/58	41	9	2,523	18	Abnorma
0112	12/ 1/58	42	10	3,287	20	Normal
0232	2/11/58	43	10	1,999	20	Norma
0382	2/12/58	40	10	2,807	20	Abnorma
0602	11/18/58	43	11	2,829	22	Norma
0072	2/ 9/58	40	11	3,090	19	Norma
0252	2/10/58	41	11	2,466	19	Norma
0332	2/14/58	40	11	2,552	18	Abnorma
0002	1/10/58	42	12	3,623	20	Norma
0172	12/22/58	40	12	3,347	21	Norm
0322	12/10/57	40	13	3,005	22	Abnorma
0012	1/15/58	41	13	2,495	20	Norm
0062	1/30/58	40	13	3,005	21	Norma
0082	1/ 1/58	34	13	2,509	22	Norm
0182	1/12/58	41	13	3,735	20	Norm
0192	2/ 9/58	38	13	3,203	20	Norm

^{*}Calculated from date of delivery for Case 0042.

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Group IV is divided for comparison. The suljects of the study were 15 to 25 months of age at the time of their final examination in 1960.

Lach child was examined carefully. The field investigator was given special training in the evaluation of the status of visual, auditory, cardiopulmonary, and central nervous systems. Growth and development were appraised by the Stuart anthropometric indices. Funduscopic findings supplemented clinical appraisal of visual acuity. Complete audiologic evaluation was obtained for any child whose auditory status was doubtful. Fifty-six consultations were obtained with specialists including ophthalmologists, cardiologists, pediatricians, and others. In addition, roentgenographic and electrocardiographic studies were obtained when necessary for diagnostic aid.

Results

At the time of the first examination in 1959, 42 abnormal or questionably abnormal children were found with a total of 60 individual or questionable anomalies. In 9 children, 19 previously suspected abnormalities were disproved on the basis of subsequent examination and/or consultation in However, 6 individual anomalies initially unsuspected were found on the second examination and consultation. These anomalies are of a serious nature, e.g., partial deafness and mental deficiency. One family with an abnormal sibling was lost from the study after its initiation. After reevaluation, there are 34 anomalous children in the entire series with a total of 47 individual anomalies. The children are distributed as follows:

Group	Total No.	No. abnormal
I. Rubella	85	14
II. Gamma globulin with- ut symptoms	84	5
III. Camma globulin with	8	2
IV. Siblings	231	13

Many have multiple anomalies involving more than one major system. Restudy of

Table VI. Siblings of rubella Group I by trimester of mother's infection with study child

Trimester	Total No. siblings	Abnormal siblings*
First	45	1 (petit mal epilepsy)
Second	36	1 (abdominal epilepsy)
Third	18	2 (congenital heart disease myelomeningocele)
Total	99	4

*All abnormal siblings fell in families with normal study

the children at older ages might change the results.

Rubella series. Table III shows the results of pregnancies tabulated by gestational week and trimester of rubella infection. The first trimester has been subdivided into two periods of 4 weeks and one of 5 weeks to aid evaluation of the significance of rubella by gestational age.

Table IV lists the specific week of infection for the 14 pregnancies resulting in an abnormal child and each abnormality found. Six of these children have anomalies characteristic of the rubella syndrome and are permanently handicapped. One child has mental retardation alone. Serious anomalies which are not characteristic of rubella effect were found in 2 other children. One has exstrophy of the bladder and hyperphalangism. Another child has cerebral palsy which followed a hard, rapid labor and breech delivery.

Two children with congenital heart lesions are asymptomatic and have a satisfactory prognosis. Polydactyly, an inguinal hernia, and a cavernous hemangioma of the left side of the face are single lesions in the remaining three.

In Cases 0362 and 0282 the infants had been in cardiac failure before reaching one year of age. Although corrective operation has improved their cardiac status, mental deficiency and other defects are irremediable and discourage restorative efforts.

Some of the data relative to all the children delivered following rubella in the first trimester are given in Table V. The calcu-

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lated week of delivery, gestational age of the rubella infection, birth weight, age of child at final examination, and result are listed. Only 3 of these children were premature by birth weight, one of whom is abnormal. Six patients were delivered at more than 42 weeks by estimated duration of pregnancy. Two of these children are abnormal and weighed 2,325 and 2,523 grams, respectively. Patient 0042 had grossly irregular menses. The last menstrual period was recorded as March 29, 1958, giving an estimated date of delivery Jan. 5, 1959. Delivery of a normal term infant occurred Feb. 28, 1959. This one gestational age at time of rubella was then re-estimated on a basis of date of delivery and birth weight.

Four abnormal children were found among the 99 siblings of the rubella group. Two have congenital anomalies and two are under treatment for epilepsy. Table VI shows the incidence of anomalies in the siblings by trimester of infection for the mother with the study child.

Gamma globulin group. Table VII gives the results of the survey of 84 children delivered after exposure to rubella and treatment with gamma globulin without subsequent rubella symptoms. One neonatal death and 4 abnormal children were found. The incidence of anomalies among those treated with gamma globulin during the first trimester in this group is not significantly different from the incidence among their siblings. One child has congenital dislocation of one hip which later improved with treatment; one case each of metatarsus varus, cryptorchidism, and umbilical hernia was

also found. One neonatal death occurred in which no anatomic abnormalities were noted at autopsy; death resulted from peritonitione hour after delivery.

Fifty-five women received 0.1 c.c. of gamma globulin per pound of body weight 17 received smaller doses, 6 larger doses, and the exact dosage was not recorded for 6. It was impossible to secure any reasonable index of previous rubella infection and natural immunity from these patients because of faulty memory concerning childhood diseases and the benign nature of rubella in childhood.

Data relative to the 8 patients who developed a rubella-like illness subsequent to exposure and gamma globulin treatment are presented in Table VIII with individual descriptions. Two abnormal children with 4 separate anomalies occurred. One is disabling since a combination of motor and mental retardation is present.

One hundred and twenty-four of the siblings in Group II were found to include 8 abnormal children (Table IX). One child with diabetes mellitus and one with splenic vein thrombosis and hypersplenism occurred in the same sibship. The study child is normal in each instance of an abnormal sibling.

Seven siblings of the children in Group III are normal, and one sibling had hypertrophic pyloric stenosis at birth.

Comment

The accumulation of prospective data concerning the teratogenicity of rubella is urgently needed to assess the significance of this disease in pregnancy. The initial reports,

Table VII. Outcome of pregnancies complicated by exposure to rubella and treatment with gamma globulin—Group II

Gestational week of exposure	Total cases	Normal liveborn	Abnormal results
1- 4	5	4	Metatarsus varus, left
5- 8	20	19	Cryptorchidism
9-13	35	33	Neonatal death
			Congenital dislocation of left hip
14-26	20	19	Umbilical hernia
27-40	4	4	
Total	84	79	5

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Table VIII. Group III—patients with symptoms subsequent to exposure and treatment

Code No.	Gestation age at time of exposure	Dosage of.	Interval from ex- posure to treatment	Gestational age at time of rubella symptoms	Symptoms	Outcome
1+11	10th week	10 c.c.	3 days	11th week	Malaise, arthralgia, fever 2 days, no rash	Dextrocardia, agenesis of pectoralis major and serratus an- terior, left
1191	10th week	2 c.c.	1 day	11th week	Malaise, arthralgia, fever, posterior auricular lym- phadenopathy, typical rash	Normal
1171	7th week (1st exposure) 12th week (2nd exposure)	10 c.c. Not treated after 2nd exposure	2 days	13th week	Malaise, fever, typi- cal rash	Normal
1561	12th week	12 c.c.	3 days	15th week	Fever, rash involving lower extremities	Normal
1701	17th week	2 c.c.	8 days	18th week	Rash involving face only, cervical lymphadenopathy	Motor retarda- tion, ?men- tal retar- dation
1461	14th week	12 c.c.	Same day	18th week (no history of 2nd exposure)	Typical rash	Normal
1641	18th week (re- exposed many times after treatment)	0.35 c.c. hyper- immune globulin	7 days	25th week	Malaise, rash involving face and arms	Normal
1761	26th week	10 c.c.	5 days	28th week	Fever, malaise, typi- cal rash	Normal

although influenced by retrospection, were of value in identifying a relationship between rubella infection and congenital malformations. The criteria for a prospective analysis have been met by few subsequent studies as has been emphasized repeatedly. 15-23

Pew authors 18, 24 have emphasized that certain abnormalities cannot be recognized satisfactorily at birth. Repeated examinations and special diagnostic studies are essential for accurate recognition of many anomalies. This has been shown so conclusively in the present study that we must doubt any report which is based on less exacting standards. Reports based on infants appraised at birth are misleading and

inconclusive. An opportunity to restudy the present subjects at school age or later, particularly for hearing, visual, and mental defects, would be invaluable.

The present study was undertaken when an epidemic of severe rubella occurred. Physicians reported that most patients had more than the usual morbidity. The qualifications for a rigid prospective study were considered, and certain obvious diagnostic limitations were apparent immediately. No absolute diagnostic method can be applied to confirm rubella infection. Until such a clinical aid is available, every study must be based on presumptive evidence. The presence of an epidemic and observation of typical

Table IX. Siblings of Group II by trimester of mother's exposure with study child

Trimes- ter	Total No. siblings	Abnormal siblings*
First	94	(malrotation of colon; diabetes mellitus; splenic vein thrombosis and hypersplenism; hydrocephalus and myelomeningocele; corneal opacity, right; unilateral agenesis of lung; agenesis of pectoralis major, right; monster—still-birth)
Second	24	0
Third	6	0
Total	124	8

*All abnormal siblings fell in families with normal study

clinical disease is reasonable evidence of rubella infection, and 'physicians generally accept the diagnosis when given a description of symptoms by the patient. Similar skin eruptions can occur with other infections, allergic manifestations, and drug reactions, and a very careful evaluation of all possibilities must be made. The verification of rubella in the present series has been described. Although 22 per cent of the cases diagnosed by a physician had an anomalous outcome as opposed to 12 per cent not diagnosed by a physician at the time of infection, this difference is not statistically significant. The results are as follows:

Documentation		No. with	
of rubella	Total	anomalies	Percentage
Physician	36	8 -	22.2
History	49	6	12.2

Greenberg²⁵ found an increased incidence of fetal death and prematurity when rubella occurred in the first 8 weeks of gestation. Prematurity occurred independent of malformations. In the present series the incidence of spontaneous abortion was not appreciably increased over that in the general population. Prematurity by weight was found in 9 of 85 infants in Group I, and one of these was abnormal. There were no perinatal deaths. None of the infants in Group II were premature. The difference in

incidence of prematurity between the two groups might be explained on the basis of over-all differences in parity and socio-economic conditions (Table II); however, no attempt was made to compare adjusted incidence figures.

Anomalous fetal development occurs as a result of genetic and/or extrinsic factors. Heredity is generally considered to be an inherent cause of anomalies. Bleeding in the antenatal period, increased maternal age, dietary and vitamin deficiences, and irradiation are a few of the reported etiological factors. Two women who contracted rubella in the first trimester had subsequent vaginal bleeding and abnormal children.

Abnormalities may also occur due to specific perinatal conditions such as birth trauma, hypoxia, and infection. The lack of specificity of anomalous development due to extrinsic factors is well documented in experimental animals. A few specific anomalies due to hormones²⁸ and antihormones^{29, 30} occur in the human. Antimetabolites such as aminopterin may cause fetal death or multiple anomalies of nonspecific type.^{31, 32}

Although the genetic causation of certain anomalies is fully established, it is impossible to obtain a complete genetic record of a large series of patients. Pure chance leads to coexistence of recessive genes in an individual to produce certain anomalies. To prove or disprove genetic causation, identification of recessive traits often requires records of many generations. Consanguinity greatly increases the probability of genetic anomalies, but this was known for only one patient in this series. Her-baby is normal. The genetic origin of polydactyly is generally accepted although the condition was not found in any other member of the family in which it occurred. The remainder of the anomalies found may occur not only spontaneously by genetic mechanism but Iso due to maternal extrinsic factors. A combination of anomalies involving more than one system in one individual suggests an environmental injurious agent rather than a single genetic factor.

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in view of the lack of knowledge concerning the exact cause of various anomalies, we are unable to assign specific cause-effect relationships to the anomalies encountered. They vary from simple metatarsus varus to devastating multiple anomalies involving several major systems, typical of the rubella syndrome. Mental deficiency is a particularly distressing observation. Every abnormality has been included in the report regardless of its significance or the likelihood that it has any relationship to rubella infection. The findings in this study weigh toward a high incidence of rubella-induced anomalies because other extrinsic factors which may have influenced the outcome of the pregnancy cannot be eliminated.

Incidence of abnormalities subsequent to rubella in pregnancy. Three of the 6 women with rubella in the first 4 weeks of pregnancy had children with typical rubella syndrome, an incidence of 50 per cent. The 28.6 per cent (4 of 14) incidence of abnormalities with rubella in the fifth to the eighth week and 26.9 per cent (5 of 19) in the ninth to the thirteenth week are of the same magnitude as results recently reported19, 20, 22, 23 although there are some differences in the nature of the anomalies included. Four of these 9 abnormal children have lesions typical of rubella effect and are seriously handicapped. Two with asymptomatic cardiac defects and one with polydactyly are not handicapped. Exstrophy of the bladder and cerebral palsy were each observed once. The relation of rubella to these conditions is highly debatable; each precludes a normal life. No serious or typical anomalies occurred in 46 children whose mothers contracted rubella after the fourteenth gestational week. Cavernous hemangiomas are usually selflimited,34 and an inguinal hernia is easily reparable.

The rate of "severe" abnormalities, as well as all anomalies, apparently declines inversely with the duration of gestation at the time rubella occurs. Each malformation typical of the rubella syndrome followed overt rubella which was typical with all classical manifestations of the disease.

Although corrected results may be viewed with suspicion, a re-evaluation of the anomalies found in this study on a basis of their severity and character changes the significance of the effect of rubella on pregnancy. Mental deficiency, blindness, deafness, and some cardiac lesions make a normal life impossible and are severe abnormalities. Asymptomatic cardiac lesions, hernias, and polydactyly usually permit a normal future or one with slight limitation and are mild abnormalities. If this concept is applied to the gross results of the present study, the incidence of severe abnormalities following rubella in the first 4 weeks of pregnancy remains 50 per cent. Unfortunately, for statistical purposes, the total number of cases in this category is small. The prevalence of serious abnormalities typical of the rubella syndrome following infection in the first trimester is as follows:

Week of rubella	Total No.	Children with abnormalities
ruvella	of cases	aonormannes
1- 4	6	3 (50.0%)
5-8	14	2 (14.3%)
9-13	19	2 (10.5%)

Incidence of abnormalities in pregnancy with rubella exposure. The 83 mothers who were exposed to rubella had 84 children for study. None of these women developed any symptoms of rubella and no serious abnormalities occurred. One neonatal death due to peritonitis and 4 mild abnormalities were found; none are characteristic of the rubella syndrome. The efficacy of the gamma globulin administered to these women as a prophylactic measure is questionable.

Eight women who received gamma globulin developed rubella or a rubella-like illness. They must be considered separately since there is the possibility that the rubella was modified by the treatment. On the other hand, they are not suitable for analysis with patients who were exposed and had no overt evidence of infection. All the infants were liveborn. Two have abnormalities not typical of the rubella syndrome. The mothers of these two developed their illnesses at the eleventh and eighteenth weeks of gestation.

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Rubella may occur without a rash as evidenced by volunteer studies by Krugman.³⁵ There have been reports^{12, 20, 26, 33, 36} of abnormalities following exposure of a pregnant woman to rubella when overt disease does not appear. In Michaels' report³³ of 95 pregnancies with exposure to rubella there were only 81 normal term deliveries. This resulted from 9 abnormalities in 8 individual infants, none of which were typical of the rubella syndrome, and 6 pregnancies which terminated in abortion or stillbirth.

The present study provides consideration of a group of women who were exposed, but also given gamma globulin. The efforts of investigators37-43 to establish the efficacy of immune globulin have been conflicting and disappointing. Korns⁴² found no protection with two lots, but using a third lot he obtained a 20 per cent attack rate in the immunized group compared with 55 per cent in the controls. The variability of rubella antibody titer in donor sera may explain the marked discrepancy in results, and the antibody titer of sera administered to the women in this study is conjectural. The impossibility of evaluating natural immunity in an adult population has been mentioned. Further, the degree of exposure or the probability of its producing the disease cannot be appraised, adding to the difficulty of evaluation of results in the present series. In order to assess the degree of protection afforded by gamma globulin, a control series of pregnant women, exposed under the same circumstances but treated with a placebo, should be included.

Abnormalities in the comparison group. Two hundred and thirty-one siblings of the study children were examined in order to provide a comparison group. None of these pregnancies were known to be complicated by rubella infection. They cannot be used as direct controls since variations in age, parity, and economic conditions exist, but their environmental and hereditary conditions are relatively constant. No half siblings were included. These children offer a control population and are a group representing the spontaneous malformation rate for this

population. A total of 213 children were born to these mothers before the birth of the various children of the study and 13 afterward. Thirteen of these children are abnormal. This is a gross incidence of 5 6 per cent.

Conclusions

1. When typical rubella occurs in the first trimester of pregnancy the incidence of fetal anomalies is significantly higher than the incidence in the comparison group of siblings. The frequency and severity of the anomalies apparently decrease inversely with the gestational age at the time of infection. The first 4 weeks are critical with a 50 per cent incidence of serious anomalies in this series. Serious anomalies occur in less than 15 per cent with gestational ages of 5 to 13 weeks and none thereafter.

2. Abnormalities characteristic of rubella syndrome were not found in the absence of overt disease in this study. No conclusions can be drawn from the present material relative to the effect of gamma globulin.

3. Repeated examinations, including special diagnostic techniques, are required for recognition of abnormalities in infants and children. Only limited conclusions can be drawn from an investigation which terminates with children under one year of age, and final conclusions may depend upon findings at maturity.

4. Rubella closely simulates other exanthematous diseases and an objective technical means of diagnosis is needed.

5. A comparison group, consisting of siblings of the study children, had a spontaneous abnormality rate of 5.6 per cent.

We wish to express our appreciation to Dr. Weston M. Kelsey, Chairman of the Department of Pediatrics, for the special training given to the field investigator. We are also indebted to North Carolina physicians for their cooperation in submitting cases for this study.

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Discussion

Dr. Harold L. Gainey, Kansas City, Missouri. The authors have pointed out again the association between rubella and the risk of congenital anomalies when the pregnant patient is victimized by the rubella virus in the early weeks of gestation. There now can be no doubt of this association. The frequency of the severe anomalie, of which congenital cataracts, deafness, cardiac anomalies, and mental retardation are the most pathognomonic, will vary from time to ime and from place to place. The introduction of prospective studies by Logan and their con inued use as herein employed has changed the predicted incidence of morbidity from those of 0 to 100 per cent to the much lower but not precisely accurate 12 per cent.

The methods used in this study are based on sound clinical criteria. The basic clinical ap-

proach with records of maternal illnesses and the follow-up of children during infancy and childhood add considerably to the stature of this study.

With respect to the possible benefit from the use of gamma globulin, one cannot reach any conclusions since the risk of attack is low from this small series and particularly in view of the wide differences in doses, i.e., 0.35 to 24.0°c.c. The author's own statement of patients' faulty memory concerning childhood diseases further reduces the validity of conclusions and this they wisely have avoided. Other studies do leave doubt as to the effectiveness of gamma globulin, even though a neutralizing antibody has been demonstrated. Saul Krugman and Robert Ward, in the July 3, 1958, issue of the New England Journal of Medicine, concluded three possible

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consequences from its administration: (1) no effect; (2) prevention; (3) modification, so that a rash does not develop, a viremia nonetheless occurring. They recommended exposure of young girls to rubella.

The presence of the disease, even without its devastating effects, brings forth some questions. Why does the virus injure some babies and not others after young women acquire rubella? Are the very young tissues forming the rudimentary organs more susceptible to virus injury during the first 13 weeks than after, or are other forcesendocrinal, tissue ground substance, or the development of reticuloendothelial elements-barriers to invasion? Or is the virus normally one that does not pass across the placental barrier, but in a minority of women, for causes unknown, multiplies in the placenta and crosses it to the growing embryo? Or is partial immunity developed in the past by mothers the moderating force?

These questions are of great interest—but no answer can be given until rubella virus can be cultivated in extrahuman hosts in the laboratory. To date this is not an accomplished fact. Carl

Habel, by use of throat washings from a chill with rubella recovered the virus in a monkey, but lost the strain. To our laboratory confreres, again, do we assign the difficult and important task of isolating and cultivating the rubella virus. With this an accomplished fact, there should be a definite possibility of a vaccine to follow, as in anterior poliomyelitis.

Dr. Lock (Closing). I want to emphasize the points we made relative to the recognition of abnormalities. In this series there were 56 consultations with ophthalmologists, neurologists, and audiologists, and there were many studies to prove or disprove the presence of an abnormality. It is quite distressing to find a child believed normal by the attending physician and the family which, on careful study, proves to be deaf or to have deficient hearing and probably mental deficiency. I do not think that we can emphasize this point enough. If our report results in reservations in acceptance of studies based on the condition of the child at birth, we will have contributed something to this subject.

The incompetent internal os of the cervix

Complications after repair

ABRAHAM F. LASH, M.D.

Chicago, Illinois

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THE literature contains many reports1-12 of series of patients with habitual second trimester abortions treated surgically during the nonpregnant and pregnant state. Various modifications4, 5, 9, 10, 12 of the original surgical techniques have been developed, particularly for use during pregnancy. The results have varied in different reports and conclusions were drawn on rather small numbers of patients. Critical statements4, 5 have been made without adequate evidence and have given rise to confusion. The confusion resulting from these reports includes whether history of previous abortion alone should be considered sufficient reason for operation and whether operation is more desirable during the pregnant than the nonpregnant state because of complications.

The specific complications which have been considered are failure of treatment to prevent repeated habitual abortion, induced infertility, and rupture of the uterus. The nonspecific complications may be infection or hemorrhage which may lead to loss of the uterus or even loss of the life of the patient. The problem of fertility and reproductivity has been studied and reported.¹³ The purpose of the following presentation is to attempt to resolve this confusion by studying the complications and their pathogenesis from the

clinical records and the pathology found in the surgical specimens.

Material and results

Ninety-five nongravid patients, who had had repeated second trimester abortions due to the incompetent internal os of the cervix, as determined by history and physical findings, and 12 gravid patients (18 to 24 weeks) with imminent abortion were treated surgically at Michael Reese Hospital.

In the nongravid group, the only complication was failure of the repaired cervix to retain a subsequent pregnancy, an occurrence in 5 patients whose case histories are given in Table I. It is most important to recognize the recurrent defect due either to inadequate correction of the original lesion or to poor wound healing, because correcting it by immediate secondary repair has resulted in successful pregnancies. In this group of 5 patients, the defects were repaired secondarily in 3, while in 2, the third repair was followed by full-term pregnancies. There were no ruptured uteri in the subsequent pregnancies or labors, no hemorrhage, and no clinically manifest infection.

The complications following the Shirodkar operations during the second trimester of pregnancy were slipping of the suture in 2 patients, hemorrhage requiring suturing and blood transfusion in 1, infection in 5, and rupture of the uterus in one. The case history of the latter patient merits presenting.

Patient B. G., 27 years old, gravida iv, para 0, entered Michael Reese Hospital on April 28,

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Presented at the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960.

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Table I. Repeated repairs of the incompetent internal os

Pa- tient	Age (years)	Gra- vidity	Parity	Date	Surgical history	Results
O. R.	33	3	0	11-23-48 11-26-48 2-1-50	Spont. abortion 16 wks.; temperature 101° First repair of incompetent os Spont. abortion 8-10 wks.; influenza; temperature 102°	Two abortions; 3 living children; one vaginal and 2 cesarean
				1-6-52	Near term spont. delivery; episiotomy; girl, 5 lb., 9 oz.	deliveries
				10-1-52	Spont. abortion 18 wks.; internal os dilated + defect	
				1-27-53	Second repair with tantalum wire	
				7-12-54	Low cervical cesarean section; boy, 7 lb., 1 oz.	
				4-6-56	Repeat low cervical cesarean; girl, 7 lb., 11 oz.	
L. T.	22	3	0	3-14-51	Spont. abortion 14 wks.; curettage; first repair (?) of incompetent os At another hospital:	Three abortions; 2 living children by cesarean section
				3-10-52	Spont. abortion 20 wks.	
				12-30-52	Spont. abortion 14 wks.	
				4-27-53	Second repair, tantalum wire sutures	
				4-28-55	Low cervical cesarean section; girl, 6 lb., 2 oz.	
				12-27-56	Repeat low cervical cesarean section; girl, 7 lb.	
D. W.	34	5	0	3-9-50	First repair (imbrication)	Three repairs; 2
				7-19-50	Spont. abortion at 16½ wks.	abortions; one
				2-16-51	Second repair, excision of scarred defect	living child by
				8-2-51	Spont. abortion 20 wks.	cesarean section
				12-19-51	Third repair, wedge-shaped excision	- 1
				7-11-54	Eleven hours of labor, low cesarean sec-	
				,	tion; girl, 6 lb., 7 oz.	
A.R.	35	4	0	5-21-51	First repair of incompetent os	Three repairs; 2
				1-27-52 2-16-53	Spont. abortion 16 wks.; second repair Spont. abortion 14 wks.; third repair, tan-	abortions; one living child by
				7-14-54	Low transverse cervical cesarean section; boy, 6 lb., 14 oz.	cesarean section
H. F.	30	5	1	1-8-52	First repair of incompetent os	Two repairs; one
		-	-	8-8-54	Low cervical cesarean section; boy, Milwaukee	abortion; 3 livin
				1-26-56	Spont. vaginal delivery; girl, 5 lb., 8 oz., Milwaukee	vaginal and 2 cesarean section
				12-7-57	Spont. abortion 22-24 wks.; girl, 1 lb., 14 oz., Milwaukee	
				1-13-58	Second repair, tantalum wire sutures	-
				7-22-59	Low cervical cesarean section; girl, 5 lb.	

1959, with a history of a 16 weeks' pregnancy and vaginal bleeding of 3 days' duration. In spite of the usual therapeutic measures, abortion occurred on May 2, 1959, after which an old longitudinal scar in the corporocervical area was excised and the wound closed. She had an uneventful recovery and was discharged on the eleventh postoperative day.

The record of the third or preceding spontane-

ous abortion was interesting. On Dec. 20, 1157, a constricting nylon gauze ribbon suture had been passed around the corporocervical junction under the vaginal mucosa while the patient was 16 weeks pregnant. She received meperidine hydrochloride* twice daily, but developed mild periodic uterine cramps. On December 24 she re-

^{*}Demerol, Winthrop Laboratories, New York 18, New York

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cived hydroxyprogesterone,* 125 mg., at 9 A.M., relaxin,† 4.0 c.c. in 500 c.c. 5 per cent glucose in witer intravenously, at 10:40 A.M., relaxin,† 2.0 c. intramuscularly, was given again at 8 P.M. On December 27, relaxin,† 2.0 c.c. intramuscularly, was repeated at 12:05 A.M., at 4 A.M., and 8 A.M., followed by conjugated estrogens,‡ 20 mg. intravenously, and hydroxyprogesterone, 500 mg. intramuscularly, at 11:30 A.M. and repeated at 5:40 P.M. The strong contractions continued, and on Dec. 28, 1957, a 17 weeks' fetus was expelled through a rent in the anterior cervical wall just above the constricting ligature. The fetus survived 2 hours. The laceration of the anterior wall was repaired. The patient made an uneventful recovery and went home on Jan. 3, 1958.

In addition to the above, a patient referred from another city with suppurative cervicitis and fistulous tract into the cervical canal from the knot of the constricting suture is reported as an example of another type of complication.

Patient D. C., 35 years old, gravida v, para 0, was referred from another city with a long tragic obstetrical history. In the early part of 1953, she was spontaneously delivered of twins at 6 months; later in 1953, she lost another set of twins at 3 months; in 1955, she aborted a 5 months' twin pregnancy. In 1957 she had a wedge excision and repair, following which she became pregnant. At 5 months, however, she went into labor and a Shirodkar circular suture was inserted. The labor continued, however, and was terminated by the delivery of the fetus. In 1958, during the fourteenth week of pregnancy, a repear Shirodkar procedure was performed and was followed by a small amount of continuous bleeding. In the twenty-eighth week of pregnamy, the membranes ruptured and she was hospitalized and subjected to the usual therapy to delay the onset of labor. In 36 hours, she went into strong labor and after 3 hours with no change in the cervix a cesarean section was performed (September, 1958) and a live baby weighing pounds, 12 ounces was delivered. A pediatrician was in attendance but the baby died 6 hours later.

When I first saw this patient on April 10, 1959, there was a thick, purulent cervical discharge which yielded Staphylococcus albus and nonhemolytic streptococci on culture. This discharge had been treated from October, 1958, by the patient's local physician with antibiotics and vaginal preparations. The patient was hospitalized and given antiseptic douches twice a day followed by nitrofurazone suppositories. After 10 days the discharge had ceased and the surgical procedure was carried out. After the vaginal wall was incised and reflected in a transverse semilunar manner, the knot of the Mersilene suture was found half the distance to the internal os. The suture was cut and removed. There was a perforation into the cervical canal. This scarred tissue was excised and 5 stainless steel sutures closed the inner half of the cervical wall, while 6 tantalum (3-0) sutures closed the outer half. A small Manchester plastic operation was performed and the vaginal wound closed. Antibiotics were used during the postoperative course, which was uneventful. The subsequent menstrual periods were accompanied by cramps. The cervix was gently dilated with a probe. When last seen Jan. 29, 1960, the patient was apprehensive but she was encouraged to try to become pregnant.

Comment

Complications in the course of any surgical procedure may occur. Although there was only one severe postoperative hemorrhage in this series, others have occurred elsewhere and hysterectomy was considered necessary in one instance.21 The significant complications of inadequate closure of the internal os and rupture of the uterus are related to the problem of wound healing of the isthmic area. This may be comparable to that of the uterine wall after cesarean section. As early as 1910, Mason and Williams¹⁴ by experimental studies showed that fibrous tissue may be less likely to rupture than muscle. Greenhill and Bloom¹⁵ in 1929, Schwarz and associates16 in 1938, and Siegel17 in 1952, from histological studies, showed conclusively that original healing of wounds in the uterus takes place by fibroblastic reaction, producing a fibrous tissue union. Later this area of fibrous tissue union shrinks and is even absorbed into

⁸Delalutin, E. R. Squibb and Sons, New York 22, New York.

[†]Crivilaxin, purified brand of relaxin, extract of pregnant sow's ovaries, The National Drug Company, Philadelphia 44, Pennsylvania.

Premarin, conjugated estrogens (equine), Ayerst, McKenna and Harrison, Ltd., New York 16, New York.

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the surrounding muscle so that later the union may appear to be by direct muscle-to-muscle union. However, all these scars are not perfect as shown by physical examination immediately after delivery¹⁸ and by hysterographic studies after cesarean section.¹⁹ Also, Greenhill and Bloom showed in their histologic study of uterine scars after cervical cesarean section that an anatomically weak scar does not necessarily presuppose inability to withstand the distention caused by pregnancy or the strain of labor.

Similar imperfect healing with inadequate scars or defects occurred in 5 instances in this series. Awareness of this possible complication is important because if it is recognized in subsequent pregnancies a repeat repair may be performed or a secondary Shirodkar operation may be carried out if effacement begins in the early part of the second trimester. The history of a febrile postoperative course may suggest the possibility of poor wound healing.

The pathogenesis of these complications may be determined by a study of the tissue of the involved area in the cervix. From our study of the pathology of 32 scars or defects in the isthmus, as recently reported, and of 2 uteri, one removed 10 years after the repair and the other at cesarean hysterectomy 3 years after repair, certain characteristic scars were noted in 28.1 per cent. These scars were of two varieties: one was a dense fibrous type composed of collagenous and hyalinized fibrous tissue containing a few thin-walled blood vessels; the other was a granulation tissue or so-called vascularized scar which was composed largely of granulation tissue containing numerous blood vessels. Other pathological findings, in 22.9 per cent of the 32 cases, included mild perivasculitis and/or small foci of chronic inflammatory cell infiltrates. In this group, there was one instance of widespread of necrotizing vasculitis. There were 4 cases of adenomyosis and 2 of small leiomyomas. The remainder of the specimens showed only the normal fibromuscular structure in a thinned area or defect. The 2 uteri revealed no scars or recognizable site of repair.

Infection in operations of the cervix mabe more common than in the rest of the uterus. The cervix may harbor pathogeni bacteria for many years with or without symptomatic manifestations. This fact is very often ignored, and surgical procedures are done in the presence of infected tissue resuling in poor wound healing, sinus formation, or serious infections.21 In the nonpregnant patient, the cervix must be treated to eliminate the infection before elective operations are instituted. However, in the pregnant state under emergency conditions when the cervix is effaced and dilating, there is a greater risk because of lack of time to overcome the latent infection. Therefore, in the presence of active labor, fever, amnionitis, or ruptured membranes, it is hazardous to attempt any operations.

Once labor is started, there is no known means of stopping it, as illustrated in the case report of Patient B. G. Any operation on the cervix during pregnancy may initiate labor. This fact should deter unnecessary operations in patients with unsubstantiated diagnosis of incompetent internal os, for every gaping cervix may not be due to an incompetent internal os and every history of abortion may not indicate the presence of such a condition. When these considerations are ignored, the course of a normal pregnancy may be interrupted.

Furthermore, if the suture is not cut or the uterus emptied by hysterotomy after the establishment of labor, rupture of uterus may occur as in Patient B. G. and in other instances related to me but not reported here.²² Hemorrhage may present an alarming situation occasionally, requiring hysterectomy for its control.²²

It is of interest to note that the patients with the repeated repairs did not have fertility or reproductivity impaired. In the series of patients reported recently there were 86 per cent term pregnancies of those who became pregnant after surgical repair. In the remainder of the series, either it was too soon after the repair for attempting conception or other factors played a part in accounting for the absence of pregnancy.

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Summary

The literature, personal communications, and the case reports of Michael Reese Hospital furnish evidence of complications following the surgical repair of the incompetent internal os of the cervix during the nonpregnant and the pregnant state. These complications are hemorrhage, infection, poor wound healing, rupture of the uterus, and on rare occasions loss of the uterus and in one reported case death. The 5 instances of inadequate repair or poor healing as complications occurred in our personal current series of 95 patients.

From pathological and bacteriological studies the reason for these complications may be found. Therefore, infection must be eliminated before operation, or it may be treated prophylactically when emergency operation is essential. The operation during the nonpregnant state is elective and can follow all surgical principles.

Operations during pregnancy, that is, the Shirodkar type or circlage procedure, is indicated as an emergency procedure and, therefore, the added risk may have to be taken. Planned circlage operations and prophylactic procedures, particularly when based on a history only, raise the question as to whether hazards to the mother and the pregnancy justify such procedures.

It is common knowledge that women with patent cervices but without defects in the isthmus may carry pregnancies to term after one or two abortions, even of the second trimester type. Therefore, it may be concluded that the wedge excision of the scar

or defect is indicated during the nonpregnant state while the Shirodkar operation is indicated in the pregnant state.

It is important to recognize the proper indications and prerequisites of each operation, in order to avoid the complications described and also to prevent these operations from being incorrectly executed and falling into disrepute. The operations do not interfere with the fertility and reproductivity¹³ if infections are overcome and the cervix rendered competent, if necessary, by repeated repairs.

Once labor is begun, the obstruction (the circlage suture material) to the effacement and dilatation of the cervix must be removed to prevent rupture of the uterus. No rupture of the repaired defect was observed in this series of patients.

Conclusions

- 1. A great responsibility must be accepted by an obstetrician or gynecologist who attempts the repair of an incompetent internal os of the cervix.
- 2. In addition to establishing the diagnosis, proper preparation of the operative field and logical surgical principles must be followed to avoid the hazards described.
- 3. Lord Bacon in one of his essays on the general factors leading to error, reassures us by saying, "It is easier to evolve the truth from error than from confusion."

I wish to acknowledge the cooperation of and express my gratitude to my colleagues, Drs. F. Rubovits, N. Cooperman, S. R. Lash, and I. Udesky for allowing me to study and use their patients' records.

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Discussion

Dr. E. Stewart Taylor, Denver, Colorado. Dr. Lash, before the Chicago Gynecological Society, Oct. 15, 1948, presented his original paper, "Habitual Abortion: The Incompetent Internal Os of the Cervix." This paper is published in the AMERICAN JOURNAL OF OBSTETRICS AND GYNE-COLOGY, volume 59, page 68, 1950. He presented his concepts of etiology and pathology and the histories of 7 patients that he successfully treated surgically for an incompetent cervix. Each of the 7 had successful pregnancies following his operations. The plastic repairs of the cervix were done on these patients while they were not pregnant. The first patient was operated on by Dr. Lash for cervical incompetence on Sept. 27, 1941. In his original paper, Dr. Lash referred to a personal conversation he had had with Dr. N. Sproat Heaney, one of his former teachers and a man of wide clinical experience. Dr. Heaney told him that he was convinced that cervical incompetence was the cause of abortion in some instances. Other than this reference to Dr. Heaney's unpublished ideas on cervical incompetence, I believe that Dr. Lash's thoughts were original and the first published on this subject. Dr. Lash has continued his work on this entity over the past 19 years. His concepts at first were not adopted. I think his contributions to the recognition and treatment of the incompetent cervical os syndrome are fundamental as well as original.

He finds himself today warning his colleagues of the possible misapplication of his concepts. He does not wish to have overenthusiasm replace sound surgical principles. From today's paper we find that Dr. Lash has performed his operation on 95 patients and, in 5 of these, surgical complications, such as hemorrhage or sepsis, caused failure of proper healing. By operating upon these 5 patients a second and a third time, success was finally attained. I was interested to learn that secondary infertility after his operation occurred in only 14 per cent of his patients. I would have supposed that it would have been higher.

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Our program for the diagnosis and treatment of the incompetent cervical os as a cause of fetal loss at the University of Colorado was reported in the Journal of the American Medical Association, volume 171, page 1312, 1959. Including the 40 patients reported on there, we now have a total of 49 patients whom we have treated for incompetent cervix. Our success rate in terms of viable infants has been 82 per cent. We have learned that gross lacerations of the cervix should be repaired and that a Shirodkar operation is not helpful in these. An encircling type of procedure is inadequate under these circumstances. Metal suture material is our choice when repairing a gross laceration of the cervix during pregnancy or in the nonpregnant individual. We do a trachelorrhaphy during pregnancy if the patient has a history of an incompetent cervix and a visible laceration, if we have not had the opportunity to repair it before pregnancy. The great majority of our surgical procedures for incompetent cervix are done on pregnant patients, with a positive history and beginning dilation of the cervix. We have used Barter's application of the Shirodkar procedure. We perform the operation only when the cervical dilatation and effacement appears. If a patient has a history that is suggestive, the cervix is inspected every one to two weeks from the second month to the end of the second trimester. If the cervix begins to dilate, the operation is done. We do not do prophylactic encircling operations on the cervix. We do not use the operation in the presence of infection, hemorrhage, visible certical lacerations, ruptured membranes, or uterine ontractions. We do not attempt to halt active hor by cervical closure. Neither do we perforn the operation on patients at or near the last trim ster of pregnancy. Bed rest is a better method for prolonging gestation in a patient in whom the cervix dilates at 27 to 28 weeks' gestation

DR. ROBERT H. BARTER, Washington, I C. Four years ago in this room our group rom

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investigation. The technique is easy, and I would recommend that someone repeat it to corroborate this effort.

Shrodkar operation for cervical incompetence and introduced his name into the American literature. During the past year, or less than three years later, someone has gone to the trouble to come a new word for the Shirodkar operation. It is now being called "circlage of the cervix," whatever that means. To the best of my knowledge "circlage" is an entirely new word. It is not in any of the latest medical dictionaries.

I rise at this time to protest against discarding the name of Dr. Shirodkar from the opera-

Wishington presented the first paper on the

I rise at this time to protest against discarding the name of Dr. Shirodkar from the operation which is undeniably his. Let us continue to call the Lash operation by its right name. Let us also continue to call the Shirodkar procedure by its rightful name. Let us continue to give the more ingenious among us their rightful recognition. Is it asking too much to suggest that we continue to give credit where credit is due?

Dr. S. Leon Israel, Philadelphia, Pennsylvania. I wish to protest against the continued use of the term which, when read casually and as used here by Dr. Lash this morning, might tend to give an erroneous impression and perpetuate what I think is a clinical error, and that is the reference to the "therapeutic dose of relaxin." If Dr. Lash has evidence that there is such a thing, would he please tell us the dose?

My second comment is in reference to Dr. Lash's mention of the work of Poidevin and Bockner in hysterography to observe the weakness of cervical scars. Within the past few weeks, I had the privilege of visiting the clinic of Poidevin at the University of Adelaide, and I would like to report that this is most impressive

DR. LASH (Closing). One can hardly determine why certain women who have been operated upon do not become pregnant. In April, 1960, I reported a detailed study before the American Society for the Study of Sterility, and in this report I gave certain reasons why these women did not reproduce. After 35, the fertility curve decreases and women are less likely to become pregnant. Some women, answering a questionnaire, said they had not conceived because they had to pay off the mortgage on their home first. Factors other than the cervical repair evidently play a role.

I heartily agree with Dr. Barter in regard to retaining Dr. Shirodkar's name on his operation. I have tried to do an imbrication operation during pregnancy and I am convinced that once the cervix is effaced the only way to close that internal os is to use an encircling suture.

There is no controversy over the procedures described by Dr. Shirodkar and myself. I think his procedure is excellent during pregnancy and mine, during the nonpregnant state. I do not think his procedure is really indicated in the nongravid state.

As to relaxin, I will not get into a controversy with Dr. Israel about that. All I know is that on this patient's chart it was indicated that she was given 4 c.c. in 500 c.c. of saline intravenously every 4 hours and this was described as a therapeutic dose.

Venous distensibility during pregnancy

A. M. McCAUSLAND, M.D.
CHESTER HYMAN, PH.D.
TRAVIS WINSOR, M.D.
ALFRED D. TROTTER, JR., M.S.
Los Angeles, California

THIS study is the first of a series of experiments designed to throw some light on the nature and etiology of varicose veins. It is also a study of the physiology of the venous system during pregnancy. It is felt that steroids affect smooth muscle of veins, allowing them to distend and this is most noticeable during pregnancy. Where there is overdistensibility, varicose veins could result.

Twenty-five years ago it was my privilege to direct a varicose vein clinic at the Los Angeles City Maternity Service. At that time varicose veins were treated in one of three ways: by the injection method, by general supportive therapy, and, in certain selected cases, by operation 3 or more months after delivery. In these groups the results were generally satisfactory but it was frustrating to find that in subsequent pregnancies there was a high incidence of recurrence of varicose veins. This convinced us that we were treating a condition with very disturbing symptoms without knowledge of all the responsible etiological factors.

The usual factors were considered, such as heredity, congenital defects, increased

blood volume and cardiac output, injury, infection, and the interference of return flow of blood from the lower extremities by pressures of the enlarging uterus. Since the investigations of McLennan,1 Burwell,2 and others on venous pressures during pregnancy, it has been generally believed that varicosities were due primarily to interference of the return venous flow by the enlarging uterus. They showed quite conclusively that femoral vein pressure was higher during pregnancy than antecubital and brachial vein pressures, which emphasized the pressure factor as being a most important one. However, this concept did not explain the presence of dilated veins in the upper part of the body. It seemed to most of us working in the clinic that there was a generalized venous distensibility which was due to some physiologic process other than the mechanical interference with blood flow. In an attempt to explain this process, the present study was undertaken.

Figs. 1 and 2 illustrate graphically part of the problem confronted. Fig. 1 is an infrared photograph of varicose veins in pregnancy in the lower extremities. Fig. 2 illustrates distensibility of veins in the upper part of the body.

Attempts were made at one time to study venous distensibility by use of infrared photography. This proved to be an inaccurate method because of indistinct vein margins and inability to measure the diameters of veins accurately.

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This study was supported by grants from the McCausland-Holmes Foundation and the Delta Theta Tau Sorority.

Presented at the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960. W

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distensibility is as follows: the subject is seated with the arm supported; the venous occlusion cuff is placed on the base of the index finger and the digital plethysmograph cup sealed in place. It is important that the finger be maintained at a position 15 cm.

complete drainage of the venous system so that each distensibility record will be initiated from the same volume.

above the phlebostatic level. This insures

Room temperature is maintained above 78° F. because low temperatures decrease distensibility. It is necessary for the subject to be comfortable, relaxed, and free from all extraneous stimuli, and it is desirable that

all the tests be done by the same technician.

The arterial occlusion cuff is placed on the upper arm; the plethysmograph cup is placed on the finger in such a way that the fingertip is close to but does not touch the end of the cup and displaces approximately a 4 c.c. volume.

Two years ago, however, an ingenious rethod of studying venous distensibility was devised by Dr. Chester Hyman⁷ and Dr. Travis Winsor. This method will be published in detail in the near future. They generously allowed us to use it in studying a group of obstetrical patients. Eleven patients have been studied during their prenatal and postpartum periods. About 150 determinations were run and the method is briefly described as follows:

The apparatus includes (1) a pneumoplethysmographic pick-up; (2) varian or other suitable recording device; (3) pneumatic finger occlusion ring and system for inflating, buffer bottle, bulb, gauge, etc.; (4) rapid inflating arm occlusion cuff which can be inflated to 200 mm. Hg within 2 or 3 bulb squeezes; (5) plastic digital plethysmograph cup; (6) plethysmoseal.

The setup is shown in Figs. 3 and 4.

The technique used in measuring venous



Fig. 1. Infrared photograph illustrating varicose veins of the lower extremities during pregnancy.



Fig. 2. Infrared photograph illustrating the increased venous distensibility in the upper part of the body in pregnancy.

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Fig. 3. Illustration of the digital plethysmograph cup, pneumatic finger occlusion cuff, and upper arm occlusion cuff.

Method

Once the setup is completed, a baseline record is made by occluding arterially and waiting for the volume to drop and stabilize at a lower level; this usually requires 30 to 60 seconds. The arterial occlusion is then released. A series of readings are then taken at venous occlusion pressures of 20, 30, 40, 50, and 60 mm. Hg (Fig. 5).

The method is to apply 20 mm. Hg presure in the finger venous occlusion cuff and allow the veins to fill with blood. Once they are full, arterial occlusion is rapidly applied with venous occlusion still in effect. The finger volume then drops to a lower volume level and stabilizes, and the normally observed vasomotor activity is absent. The distance from the base line to this point is used to calculate the volume at 20 mm. Hg. This procedure is repeated at the other venous occlusion pressures. At 60 mm. Hg, once the arterial occlusion record is obtained, the venous occlusion is released (instead of arterial), which allows the finger to drain. and a final base line is thus recorded. Standardization is accomplished at this point by introduction of a known volume of air into the system, and one record is completed. Three complete recordings are made at each testing.

Calculations

A line is drawn between the initial and final base lines of the record (Fig. 5). The vertical distance from this line to each

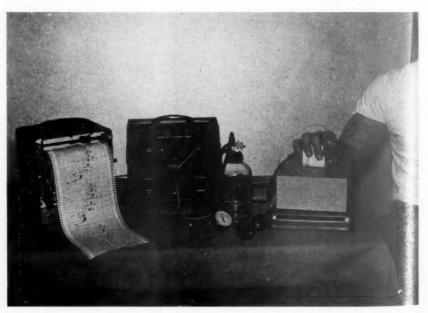


Fig. 4. Illustration of the entire apparatus used. From left to right: Varian recorder with graph, pneumoplethysmographic pickup, buffer bottle, pneumatic finger o clusion ring with inflating system, digital plethysmographic cup and arm occlusion suff.

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volume level is recorded. The standard is noted by measuring the length of the standard mark. If the standards of all three runs are the same, the distensibility values may be averaged at this point before they are converted to volume values. If the standards are different, volume values must be calculated before averaging. The volume is calculated by the formula: Finger vol. (nm.³) =

The distance value is the vertical distance between the base line and the volume record; and, in the case of the standard, the distance traveled by the writer when the standard was introduced. This can be represented in millimeters or by the divisions on the chart paper.

These calculated volumes are now plotted on graph paper, volume change on the ordinate and pressure on the abscissa, giving the distensibility curve.

Distensibility values for tabulation are

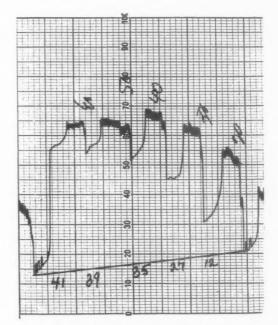


Fig. 5. Illustration of a typical distensibility graph.

obtained in the following manner: The point of intersection of the curve with the abscissa is designated as zero pressure; 30 mm. Hg pressure from the zero point was arbitrarily

					MONT	H OF P	REGNA	NCY		D	EL.	POS	TPARTU	M
Subject	Grav- ida	Para	2	3	4	5	6	7	8	9	2 days	4-5 days	6 wks.	8-16 wks.
1 (N)	3	2					1.21	1,27	1.31	1,66		1.01	0.71	
(2	2	1		0.56	1.19	0.75	0.62)					1.36		0.58
3 (N)	1	0			0.72	1.13	0.78	1.15	0.87			1.05		0.45
4 (N)	2	1				1.99	0.98	1.42	1.13	1.26			0.86	
5 (N)	1	0				1.56	1.51	0.98	1.40	1.84		1.60		0.76
6 (٧٧)	3	1					1.10	1.01	1.18	1.31	1.31	1.08		
(7	2	1	0.66	1.13	1.60	Abo	orted)						1.25	
8 (N)	2	1								1,14		0.78	0.96	
9 (٧٧)	2	1								2.36		1.36	0.91	1.14
10 (VV)	4	3						2.26	1.62	2.16		1.10	0.80	0.84
11 (٧٧)	5	3			1.62			2.04					0.95	
Averages			0.66	0.84	1.28	1.36	1.03	1.45	1.25	1.67	1.31	1.16	0.92	0.75

Fig. 6. All the distensibility values taken at 30 mm. Hg at the different stages of pregnancy. Designated in this study are patients with varicose veins (VV) and those without varicose veins (N).

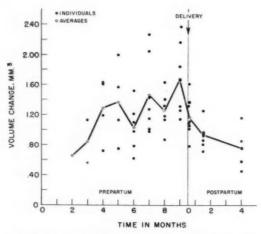


Fig. 7. Distensibility values taken at 30 mm. Hg.

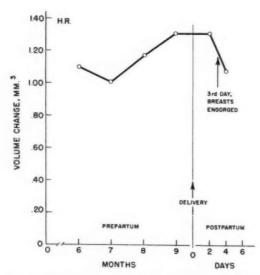


Fig. 8. Distensibility values taken at 30 mm. Hg.

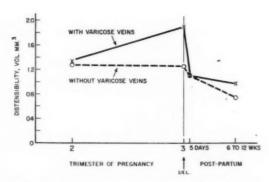


Fig. 9. Comparison of venous distensibility in pregnancy (4 patients with varicose veins and 5 without varicose veins).

chosen. The volume which corresponds to this pressure is used to represent the distensibility of the subject at the time of the particular test.

Results

Fig. 6 is a table of all the distensibility values taken at 30 mm. Hg. It designates those with normal veins and those with varicose veins. It also shows the number of cases used and the number of distensibility values taken and when during the pregnancy they were taken.

Fig. 7 is a scattergraph of distensibility values taken at 30 mm. Hg throughout pregnancy and during the postpartum course. There tends to be a gradual increase in venous distensibility as pregnancy progressed, reaching a peak just prior to delivery. At this time the average maximum distensibility is about 150 per cent above normal. There is a rather sharp decrease in distensibility on the fourth postpartum day with a gradual return to normal by the eighth to the twelfth week.

Fig. 8 is an individual case study. It was felt that this was important in that the usual distensibility curve was present; however, a test was run on the second postpartum day and there was no decrease in distensibility. On the third day, the breasts became engorged, signaling a marked decrease in estrogen levels, and on the fourth postpartum day the distensibility value dropped in the usual manner. It appears from this illustration that the breaking point in distensibility occurs between the second and fourth postpartum days.

Fig. 9 compares venous distensibility in 9 pregnant women, 4 of whom had variouse veins and 5 who did not. (Two of the original series of 11 were not included because the third trimester distensibility records were not obtained.) The reading represents averages in distensibility at the end of the second and third trimesters as well as during the postpartum period.

It is obvious from Fig. 9 that patients who have varicose veins in pregnancy lave a marked increase in distensibility as com-

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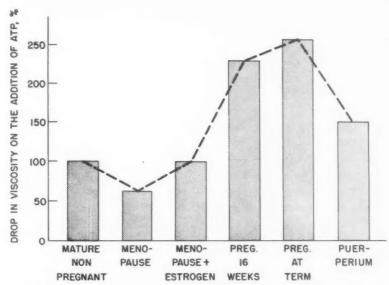


Fig. 10. Actomyosin of the human uterus in different endocrine conditions. (After Cretius, 1957.)

pared with those who do not have varicose veins. Therefore, it may be that patients with increased distensibility are more prone to develop varicosities.

The results shown in Fig. 6 were subjected to statistical analysis. Nine cases (5 normal patients and 4 with varicose veins) had distensibility measurements during the third trimester and again on the fourth postpartum day or later. The average distensibility measurements in the normal individuals were 1.25 in the third trimester and 0.90 post partum, while in those with varicose veins the corresponding measurements averaged 1.90 and 1.02, respectively. In each group the change in venous distensibility after delivery was statistically significant at the 0.02 level of probability. During the third trimester, venous distensibility in those with varicose veins was substantially and significantly higher than in the normals (p = 0.05), but the difference between the two groups post partum was negligible and lacked significance.

Comment

From these studies it seems evident that there are factors contributing to the distention and overdistention of veins in pregnancy besides the mechanical pressures of the enlarging uterus and the other etiological factors mentioned earlier. It is believed that veins distend throughout the entire body in much the same manner as they do in the fingers.

The mechanism of smooth muscle relaxation and contraction is a most complicated and intriguing phenomenon. Many basic physiologic factors are involved including the interrelationship of actomyosin, adenosine triphosphate (ATP), and ions which cause muscle fibers to react. There is much

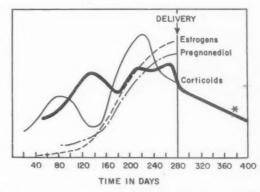


Fig. 11. Hormone levels during pregnancy. (After Venning.) Heavy curve (*) represents distensibility values taken at 30 mm. Hg.

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in the literature that supports the view that steroids affect the smooth muscle in blood vessels.

In the first place, Foote³ has found that three to four times as many women as men have varicose veins, and states that "puberty, pregnancy and the menopause with their attendant endocrine disturbances doubtless have something to do with this finding."

Reynolds⁴ has shown that in oophorectomized rabbits the veins in the ears dilate when estrogen is given.

Also it would appear that the work of Cretius,⁵ Csapo⁶ and others is basic in understanding venous distensibility in pregnancy. Csapo⁶ has shown that estrogen increases actomyosin in smooth muscle fibers. Their work substantiates the concept that steroids affect smooth muscle.

Fig. 10 illustrates graphically the amount of actomyosin in the human uterus under different endocrine conditions.

Fig. 11 shows how the venous distensibility curve parallels the steroid curves of pregnancy.

Steroid determinations in blood and urine would have been a valuable adjunct to this study but were not feasible at that time. The exact steroid fraction or combination of fractions responsible for the distensibility is not as yet known and is an interesting objective for further investigation.

One may theorize that the smooth muscle in other organs such as the gall bladder, the genitourinary tract, bowel, etc., may be affected in a like manner by steroids. Overdistensibility of these organs is frequently observed during pregnancy.

One of the practical applications emerging from this study is the advisability of postponing varicose vein operations until the eighth to twelfth week post partum, when veins have involuted and distensibility has returned to normal. This could also apply to operations contemplated on other smooth muscle structures. This is mentioned because there seems to be a trend to do immediate postpartum vein operations for economic reasons.

Since steroid imbalance may be an etiological factor in varicose veins, the correction of this imbalance by the use of steroids may some day be valuable in the treatment of varicose veins.

Summary

- 1. There is a 150 per cent increase in venous distensibility during pregnancy which returns to normal at about 8 to 12 weeks post partum.
- 2. Patients with varicose veins have greater venous distensibility during pregnancy than those without varicose veins.
- 3. Evidence is presented that steroids affect smooth muscle in veins. Other smooth muscle structures may be affected in a like manner.
- 4. It is believed that increased venous distensibility is another etiological factor in the development of varicose veins.
- 5. It seems logical to postpone varicose vein operations until venous distensibility has returned to normal at the eighth to twelfth week post partum.

We are indebted to Frederick J. Moore, M.D., Professor of Public Health, for assistance in analysis of the data. Equipment was donated by the Department of Physiology, University of Southern California, and the Heart Research Foundation, Incorporated.

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Discussion

DR. MILTON L. McCall, Pittsburgh, Pennsylvania. We are all pretty well cognizant of the serious import of varicose veins, which not only are a prominent cause of morbidity and disability but also, through their complications, may sometimes even cause death. It is important to note that until the age of 20 years the incidence of varicosities among the two sexes is approximately the same, but that during the childbearing period the ratio suddenly changes and women outnumber men four to one.

Dr. McCausland's first publication on the subject appeared more than 20 years ago. He was one of the first to suggest the possibility of a hormonal relationship to the etiology of varicose veins.

Even though this is a preliminary study, it is noteworthy that Dr. McCausland and his associates have demonstrated that there is an increase of 150 per cent in venous distensibility during normal pregnancy and that this change disappears by about the eighth week post partum. Furthermore, pregnant patients with clinical evidence of varicose veins have a much greater degree of venous distensibility. It would be of great interest to know if there is a tendency toward increased distensibility measurable by the new method in patients without clinical evidence of varicosities but who subsequently develop this condition.

We now are on the threshold of the development of new and resourceful ways of determining minute amounts of hormones in the blood and other body fluids and tissues. Such investigations combined with evaluation of venous distensibility by the method described here today would certainly make a most exciting research project.

I)R. Russell R. De Alvarez, Seattle, Washing on. I am particularly interested in one of the comments made by Dr. McCausland relative to the increase of actomyosin in pregnancy. Actomyosin is a protein complex made up of two separate proteins: actin and myosin. Most studies on the biochemical properties and the molecular

concepts of these two substances have been carried out on striated muscle. To my knowledge, practically nothing is known about the actin or myosin content and metabolism of the uterine muscle cell, except for the work performed and quoted by Csapo.

In a serial study of the proteins carried out during normal pregnancy, using paper electrophoresis and more recently starch gel electrophoresis of the serum of normal pregnant patients, we found a decrease in most of the protein fractions with the exception of a rise in the beta globulin and of fibrinogen, of course, which is well known.

Dr. McCausland shows a parallelism between venous distensibility and the progressive rise in estrogen during normal pregnancy. Estrogen is classified as a lipid and belongs to the general class of derived lipids. Since the beta globulin is the protein fraction that does increase and since the steroids are usually, or I should say more frequently, attached to the beta globulin fraction, could not the rise be due not only to the steroids but to a combination of lipoproteins? We have, in the starch gel electrophoresis, found that there is a protein which seems to be characteristic of pregnancy, is found in no other situation, and disappears after the completion of pregnancy. At our present stage of investigation we do not know exactly when this begins but it seems to make its appearance about midpregnancy. Of course, varicose veins in pregnancy make their appearance considerably earlier, certainly earlier than the stage at which pressure, which is often used as an explanation to the patient, becomes a factor.

Could it not be, then, that a multifaceted relationship exists among protein metabolism, lipid (steroid) metabolism, and venous distensibility?

DR. McCausland (Closing). I believe, Dr. de Alvarez, that there may be a relationship between the serum lipids, steroids and smooth muscle. We know very little about the true relationship of steroids to smooth muscle.

Cesarean section in Cincinnati, Ohio, 1950-1959

RICHARD D. BRYANT, M.D.

Cincinnati, Ohio

IN 1955 I reported a statistical analysis of all the cesarean sections performed in the city of Cincinnati in the 5 year period 1950-1954. That study was continued for 5 more years, 1955-1959. The findings of this second 5 year period and the combined results of the 2 periods constitute this paper.

Cincinnati has a population of roughly 500,000, the metropolitan area about 750,000. About two thirds of the deliveries in Cincinnati hospitals are for actual residents of the city; the other one third come into the city from up to 40 miles away. The operations were performed in 9 different hospitals. I estimate that in Cincinnati well over 95 per cent of all patients with a previous cesarean section are delivered by section in all subsequent pregnancies.

The definition of cesarean section is the same as used in the previous paper.¹ "Cesarean section is the operation in which one or more babies weighing 500 grams or more are removed from an unruptured uterus through incisions in the abdominal and uterine walls."

The method of study was the same as previously used. I personally abstracted the chart of every patient who underwent cesarean section in the entire city. Analyses of the findings make up this report.

Incidence

Table I, showing the incidence of section, reveals that while the incidence of both pri-

From the Department of Obstetrics, University of Cincinnati College of Medicine.

Presented at the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960. mary and repeat sections has increased the incidence of repeat sections has increased more. This is probably because of larger families, almost no increase in the incidence of vaginal delivery following section, and a distinct trend away from routine sterilization following some arbitrary number of sections (Table XIII). Thus, in the first 5 year period, 25 per cent of the repeat sections were the third or later sections, while in the second period 35 per cent were.

Operators

These 6,265 operations were performed by 84 physicians in practice plus 35 or more residents. Of the private physicians, 59 were recognized specialists, the remainder being general practitioners and surgeons. The specialists performed 97.4 per cent of the operations in the first period, 98.2 per cent in the second period. Table II shows who performed most of the operations.

Indications

The indications for the section are shown in Table III. When multiple indications were present the most urgent was used for the purpose of this classification. All previous sections were listed under that category, no matter what complications were present. This and other factors, such as errors in diagnosis, cause a numerical difference in the number of cases listed here as compared with the totals in various special categories considered later.

While the basic distribution of indications has remained approximately the same over the years, a few minor shifts have occurred, many as the result of new concepts originally

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Table I. Incidence of cesarean section in Cincinnati

	1950-1954	1955-1959	1950-1959
Total deliveries	101,182	120,527	221,709
Total sections	2,486	3,779	6,265
Incidence of section (%)	2.46	3.13	2.83
Total primary sections	1,467	2,082	3,549
Incidence of primary section (%) 1.46	1.83	1.62
Total repeat sections	1,019	1,697	2,716
Per cent repeat sections	41	45	43

presented by members of this association. For instance, there was significant increase in trial forceps followed by section; in early section in selected cases of Rh incompatibility and diabetes; in delivery by section when preinvasive carcinoma of the cervix was present; and when cervical circlage had been performed. Cesarean section for toxemia decreased a great deal, chiefly because of the decrease in the incidence and severity of this complication.

Type of section

While nearly all types of sections were done occasionally, 92 per cent were of the lower segment type. A transverse incision (or blunt muscle-separating maneuver) was used in 80 per cent of these. Extraperitoneal and peritoneal exclusion techniques were used once or twice a year, chiefly for teaching purposes. Cesarean hysterectomy was done mainly because of bleeding but, except for 2 cases, not because of infection. There were a few hysterectomies for the purpose of sterilization. A classical incision was used when extraordinary speed seemed advisable, when adhesions or fibroids blocked the approach to the lower segment, or when large varicosities involved the lower part of the uterus.

Anesthetics

The anesthetic of choice (87 per cent) was spinal, usually Pontocaine in doses of 5 to 10 mg., given as a single injection with the patient lying on her side. Next most common were cyclopropane and nitrous oxide-oxygen-ether. The sole death due to anesthesia resulted from aspiration of vomi-

tus during an emergency section done under Pentothal-curare-nitrous oxide-oxygen.

Complications

Major complications at the time of cesarean section were relatively few. The bladder was entered 8 times. All 8 wounds healed without incident. Uterine atony necessitated immediate hysterectomy in 17 cases and delayed hysterectomy in one (Table IV). In 4 cases uterine flaccidity hemorrhage threatened to necessitate hysterectomy but were overcome by clamping (one case) or ligation (3 cases) of the uterine arteries. Abnormally adherent placentas made immediate hysterectomy necessary in 3 cases. In 6 others the placenta was removed by blunt and sharp dissection, only to be followed in hours or days by severe bleeding requiring hysterectomy. One of these was a case of placenta percreta in which placental tissue had penetrated the entire thickness of the uterine wall and had extended to the bony pelvis. Tearing of the lower uterine segment with hemorrhage necessitated hysterectomy or salpingectomy four times. Minor tears occurred rather frequently. One patient died of hemorrhage

Table II. Cesarean sections performed by * individual obstetricians

No. sections performed	No. operators
463	1
200 or more	9
100 or more	17
70 or more	25
	(83% of all sections)

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Table III. Indications for cesarean section

Class 1. Mechanical obstruction	to delivery	1,287
A. Maternal (bony plus		
obstructing tumors)	1,004	
B. Fetal (presentation and		
position)	2 8 3	
Class 2. Bleeding		975
A. Placenta previa	554	
B. Premature separation of the		
placenta	404	
C. Low-lying placenta	10	
D. "Bleeding"	7	
Class 3. Hypertensive diseases		141
A. Toxemia	112	
B. Chronic hypertension with	or	
without toxemia	20	
C. Eclampsia	9	
Class 4. Fetal indications		297
A. Prolapsed cord	100	
B. Fetal distress	80	
C. RH incompatibility	31	
D. Diabetes	76	
E. Postmaturity	10	
Class 5. Functional abnormaliti	es (uterine)	521
Class 6. Abnormalities of the p	elvis organs	149
Class 7. Concurrent and intercu	irrent disease	s 38
Class 8. Miscellaneous		141
Total primary sections		3,549
Total repeat sections		2,716
Total sections		6,265

due to postoperative atony of the uterus and another because of the development of an enormous retroperitoneal hematoma (Table VII). The placental site was sutured three times. Wound dehiscence occurred five times. All were sutured promptly, and all healed rapidly. There were 5 wound abscesses, and, postoperatively, one tuboovarian and one pelvic abscess. No patient died of infection. Ileus rarely developed. Minor wound hematomas did not develop as often as did para-

Table IV. Serious bleeding complications and their treatment

Atony		23
Immediate hysterectomy	17	
Late hysterectomy	1	
Clamping of uterine arteries	1	
Ligation of uterine arteries	3	
Postoperative (death)	1	
Broad ligament and retroperitoneal		
hematoma (one death)		4
Adherent placenta		9
Immediate hysterectomy	3	
Delayed hysterectomy	6	

vaginal hematomas following vaginal de-

Pulmonary embolism was in every case unanticipated. In 2 fatal cases it occurred in less than 12 hours after operation; in the other 2 literally weeks after delivery. It is possible, even probable, that nonfatal embolism occurred a dozen times or more.

Renal failure, temporary or fatal, was usually related to toxemia, shock (usually due to hemorrhage), or transfusion reaction.

Morbidity and antibiotics

Morbidity was defined as the development of an oral temperature of 100.4° F. or higher during 2 or more 24 hour periods after delivery, excluding the first 24 hours, temperatures being taken every 4 hours around the clock. It has been of major interest to obstetricians for more than 25 years. In none

Table V. Morbidity rates with various conditions

Classification	Morbid- ity rate (%)	No.
All cases	14	6,265
Elective section	8.4	2,218
Patients 17 years of age or less	44	158
Patients 40 years of age or		
more	10	327
Prolapsed cord	26	105
Transverse lie	23	243
Placenta previa	17	597
Premature separation of		
placenta	18	+39
Incidental appendectomy	8	193
Failed attempt at vaginal		
delivery	27	60

of our hospitals are temperatures routinely taken this often, so no claim of scientific accuracy is made for the morbidity figures which follow. On the basis of the frequency and accuracy with which the temperatures were taken in this series, 14 per cent of the patients were morbid. The findings in selected groups are shown in Table V.

Without making any allowance for factors which might conceivably influence the figures, it seems reasonable to assume that the morbidity rate in purely elective cesurean

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	Morbidity (%)			
Type of case	White patients	Negro patients		
Elective sections	6.5	25		
All sections	12	33		
All sections, private hospitals	12	29		
All sections, charity hospital	25	34		

section should be the most favorable and should indicate the basic rate which could be expected simply on the basis of performing a transperitoneal hysterotomy on a normal patient. With use of this criterion—cesarean section on a normal patient supposedly near term, with a living baby in an unruptured uterus, membranes intact, and not in labor—the morbidity rate was 8.4 per cent (187 instances of morbidity in 2,218 patients).

An interesting facet of the morbidity problem was the discovery that Negroes consistently had a higher morbidity rate than whites (Table VI). For elective sections the figures were 25 per cent versus 6.5 per cent. For all sections the figures were 33 per cent versus 12 per cent. Suspecting that the locale of the delivery might be a factor, we found that Negro women delivered in private hospitals became morbid two and one-half times as often as did white patients in the same hospitals. In the large charity hospital, Negro patients were morbid half again as often as white patients. The conclusion appears inescapable that Negroes develop significant fever after cesarean section more often than whites. The reason for this is not known.

The use of antibiotics prophylactically after elective section was followed by a morbidity rate of 6.4 per cent; when antibiotics were not used prophylactically the morbidity rate in similar cases was 9.6 per cent. Because of publicity concerning the danger and futility of the indiscriminate use of antibiotics, because of serious and even fatal cases, locally, of drug sensitivity and the development of fatal infections from resistant organisms even when antibiotics were given prophylactically, and perhaps for other reasons, the use of antibiotics prophylactically

Table VII. Maternal mortality after cesarean section*

Cause of death		No. cases	
Cancer (breast, cervix, melanoma)		3	
Cerebral hemorrhage (present on admission)	1		
Poliomyelitis	1		
Malignant hypertension (death 85 days after	1		
Rupture of aneurysm of circle of Willis (posto	1		
Cardiac failure (60 days after operation)		1	
Pituitary tumor		1	
Multiple sclerosis (101/2 months after operation	n)	1	
Ergot reaction		2	
Anesthesia		1	
Shock (no findings at necropsy)		1	
Hemorrhage		2	
Postoperative uterine atony	1		
Retroperitoneal hematoma	1		
Renal failure		3	
Bilateral cortical necrosis of kidneys	1		
Following severe shock and hemorrhage	1		
Unexplained (possible transfusion reaction)) 1		
Embolism (pulmonary)		4	
Twenty-four days after operation	1		
Twelve hours after operation	1		
Eighteen days after operation	1		
Four hours after operation	1		
Total		23	

^{*}Deaths within one year of cesarean section.

has dropped from 46 to 24 per cent in elective sections. This has not been accompanied by a corresponding increase in morbidity.

When the results from individual hospitals were analyzed, it was found, as expected, that morbidity rates were significantly higher in some hospitals than in others. In those hospitals with the highest rates, prophylactic antibiotics appeared to have real value. Where morbidity rates were lowest, the prophylactic use of antibiotics was of questionable value, even to the extent that in some years patients receiving prophylactic antibiotics had a higher morbidity rate than those who did not.

Maternal mortality

Twenty-three of the patients are known to have died within one year of cesarean section. The causes of death are listed in Table VII. In the first 10 cases it is unlikely that the method of delivery contributed in any way to the death. The outcome would probably have been the same had vaginal delivery been elected. The probable ergot deaths were mentioned here previously. No similar deaths have occurred since the virtual abandonment of the routine administration of ergot intravenously following section under spinal anesthesia. The absence of deaths due to infection should be noted. I-and no doubt you-am sometimes asked: "What is the maternal mortality rate in cesarean section?" I am unable to give an intelligent answer to this question.

Perinatal loss

There were 6,338 babies delivered by cesarean section, including 71 sets of twins and one set of triplets. The gross perinatal less was 7.6 per cent. Among babies alive on admission to the hospital, the loss was 5.6 per cent. Table VIII shows the perinatal less rates by weight groups.

Diabetes

There were 135 diabetic mothers and, including twins, 140 babies. Perinatal loss was 22 per cent. Twins were encountered two and one-half times as often as would be expected. The significance of this is not known. A distressingly large number of babies were alive at the time of the admission of the mothers to the hospital but died prior to operation. This suggests the possibility that psychogenic factors may precipitate intrauterine death in diabetics. No maternal deaths occurred.

Placenta previa

Placenta previa was present in 597 patients. In 17 of these cases no bleeding had occurred, placenta previa being found incidentally at the time of cesarean section for some other indication. There were 7 sets of twins, so 604 babies were delivered. Gross uncorrected fetal loss was 15.4 per cent. No baby weighing less than 1,000 grams survived. Perinatal loss by weight groups is shown in Table IX. Twelve of 22 stillborn infants were dead on admission of the mothers to the hospital. Of the babies alive on admission, 12.7 per cent were lost. Maternal morbidity was 17 per cent. X-ray examinations to determine the location of the placenta were used in 22 per cent. The lower segment operation was used in 67 per cent of the cases. In spite of the fact that some

Table VIII. Perinatal loss in all sections

Weight group (grams)	No. babies	Loss rate
500-1,000	27	92
1,001-1,500	90	67
1,501-2,000	254	32
2,001-2,500	580	19
More than 2,500	5,375	3.6
Unknown	12	
Total	6,338	

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Table IX. Perinatal loss in cases of placenta previa

Weight group	Total	Perinatal loss		
(grams)	babies	No.	%	
500-1,000	4	4	100	
1,001-1,500	30	18	57	
1,501-2,000	78	28	36	
2,001-2,500	130	24	18	
More than 2,500	357	15	4.2	
Unknown	5			
Total	604			

anesthesiologists decry the use of spinal anesthesia where there is actual or potential hemorrhage, spinal anesthesia was used in 74 per cent of the cases. There were 2,176 patients in the entire series who previously had had a cesarean section. Placenta previa was present in 31, or 1.1 per cent of these patients. This will be commented on later. One mother died, of ergot reaction, a maternal mortality rate of 0.17 per cent.

Premature separation of the placenta

Premature separation of the placenta was present in 439 cases, yielding 446 babies. Gross uncorrected fetal loss was 35 per cent. However, in the first 5 year period it was 41 per cent, only 32 per cent in the second. The improvement can probably be attributed to earlier intervention. The lower segment incision was used in 87 per cent of the cases. Spinal anesthesia was employed in 65 per cent. The morbidity rate was 18 per cent. Among 226 term-sized babies, 22 per cent died; of 220 premature infants, 48 per cent failed to survive.

Dr. James Porter³ recently reported, from Grady Memorial Hospital (Atlanta), a series of 283 cases of abruptio placentae, the majority of which were managed by vaginal delivery. In his series, of babies alive at the time of admission of the mother to the hospital. 55.7 per cent left the hospital alive. In the Cincinnati series (all patients delivered by co arean section), 81.5 per cent left the hospital alive. No baby weighing less than 1,000 grams survived, and only 9 of 27 weighing between 1,001 and 1,500 grams lived.

Of the 439 mothers in this series of pre-

mature separation of the placenta, 4 died, 2 of renal shutdown, one of postoperative atony and hemorrhage, and one of aspiration of vomitus (anesthesia). This mortality rate, 0.9 per cent, compares favorably with the Grady Memorial rate of 1.8 per cent.

In 33 cases of premature separation of the placenta, as diagnosed at section by visual determination of the location of the placenta, of the location of the separated portion, by the presence of old clot in the upper part of the lower uterine segment or even the fundus, by mottling of the uterus, and by clinical signs such as point tenderness of the uterus, the location of the placenta in the uterus was that of placenta previa. This point was commented on in a previous paper.

Of the 439 mothers involved, 33 had previously undergone cesarean section.

Prolapsed cord

Prolapsed cord was the indication for operation in 105 patients. Perinatal loss was 21 per cent (22 babies). None of 6 babies weighing less than 1,500 grams survived. Maternal morbidity was 26 per cent. Presentation was breech in 32 cases, transverse in 20, vertex in 42, compound in 3, and not stated in 8. General anesthesia was used in 65 per cent of the cases. This is in sharp contrast to the 12 per cent incidence of general anesthesia in the entire series. There were no maternal deaths.

Transverse lie

Cesarean section was performed because of transverse lie in 243 cases. The cord had prolapsed in 8 per cent. Placenta previa was present in 11.5 per cent. None of the babies

Table X. Fetal mortality in cases of transverse lie

	Buffalo series ² (vaginal deliveries)	Cincinnati series (cesarean sections,
Total babies	133	247
Single babies weighing more than 1,000 grams	80	238
Total sections	13	238
Total vaginal deliveries	67	00
Gross fetal loss, single, 1,001 grams or more	29	31
Gross fetal loss rate, single, 1,001 grams or more	43%	13%

weighing less than 1,500 grams survived. X-ray examination was used to confirm the clinical impression of the presentation in 43 per cent of the cases. The lower segment type of incision was used in 83 per cent. In 8 of the 114 cases in which a transverse uterine incision was used, a secondary midline longitudinal incision ("T" incision) was required.

The gross uncorrected fetal loss for all 247 babies was 36, or 14.6 per cent. Winkler and Cangello² recently reported a series of patients with transverse lie presentations delivered vaginally in Buffalo. In their series 8 of 42 mature babies who were alive at the time of admission succumbed, a perinatal loss of mature babies of 19 per cent. In 173 comparable cases being reported here, the perinatal loss was 10, or 5.8 per cent. The gross perinatal loss in the Buffalo series, corrected only for twins and for babies weighing less than 1,001 grams, all vaginal deliveries, was 43 per cent. Comparable cases, all deliveries by cesarean section in Cincinnati, resulted in perinatal loss of 13 per cent (Table X).

There was one maternal death among the 243 mothers; this was due to the development, postoperatively, of a tremendous retroperitoneal hematoma.

Repeat sections

There were 2,716 repeat sections, or 43 per cent of all the sections. There were 28 sets of twins, so 2,744 babies were delivered. Of these, 91 or 3.3 per cent failed to survive. Perinatal loss was slightly greater in the second period than in the first period, due chiefly to the increased number of sections in diabetic patients and where Rh incompatibility existed. For unknown reasons there

was also a slight increase in the loss of apparently normal babies. Seven mothers died, 2 of ergot reaction, one of pituitary tumor, one of cardiac failure (60 days postoperatively), and 3 of pulmonary embolism.

The repeat section was performed electively in 75 per cent of the cases. There were 7 sets of twins, so 2,040 babies were delivered electively. Since by the definition used here elective section implies a live baby, there were no stillborn infants. Twenty-four or 1.3 per cent of these babies died neonatally. Corrected for 8 babies with congenital anomalies incompatible with life and one who died of chloramphenicol poisoning, the fetal mortality rate in elective repeat section was 0.8 per cent.

Of the babies delivered by elective repeat section, 4.8 per cent were premature by weight. Thirteen of these died, a mortality rate of 12 per cent. For mature babies delivered by elective repeat section, the uncorrected fetal loss was 0.6 per cent.

Because of the relatively high fetal death rate among premature infants mistakenly delivered by elective repeat section, there is feeling in some quarters that repeat section

Table XI. Indications for elective suture section

Indication	No. patient
Previous section	1,879
Disproportion	123
Uterine scars other than section	29
Previous vaginal repair	28
Previous obstetrical difficulty	25
Various others	134
Total	2,218

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should not be performed electively, but rather that the onset of labor, rupture of the membranes, or some emergency (such as bleeding) makes immediate section mandatory. One of the claimed advantages of vaginal delivery in pregnancies following section is the avoidance of delivery of premature babies who might die neonatally because they were delivered too soon. An attempt was made to determine whether or not awaiting labor or other emergency seemed to improve the perinatal salvage rate. After eliminating patients with diabetes and Rh incompatibility it was found that 601 patients were not operated on electively after the baby reached a weight of 2.500 grams, but, rather, the section was done because the baby had died or labor or some emergency had occurred. Eleven of these babies did not survive-7 were stillborn and 4 died neonatally. Ten of the 11 babies were normal, yielding a corrected perinatal loss rate of 1.7 per cent, about double the corrected perinatal loss rate for elective repeat section and nearly triple the perinatal loss rate for normal term babies. One other catastrophic event can occur. This is rupture of the uterus. While no detailed study of this complication was made, I do know that at least 4 mature babies were lost during the 10 years because of rupture of the scar of a previous section. When these are added to the 10 babies lost in connection with emergency repeat section (as opposed to elective repeat section) the perinatal loss rate becomes a minimum of 2.3 per cent, and it may well be greater. To me the conclusion is inescapable that elective repeat section carries with it a lower perinatal loss rate than does emergency repeat section.

Elective sections

Some aspects of the results of cesarean section can best be determined by a study of the results obtained in elective sections. With this in mind, the elective sections in this series were analyzed. In this connection, elective section meant the performance of section (1) at a predetermined time; (2) on a patient whose baby is supposedly alive

and mature; and (3) where no associated condition which might influence the outcome for the mother (such as toxemia, cancer, high blood pressure, heart disease, diabetes) or baby (Rh incompatibility, diabetes, postmaturity, labor, ruptured membranes) is known to be present. There were 2,218 such patients in this series. The indications for the sections are shown in Table XI.

Of the 2,228 babies obtained, 5.2 per cent were premature by weight. Total uncorrected neonatal loss (there were, of course, no stillbirths) was 1.2 per cent. Corrected for congenital anomalies, the rate was 0.7 per cent. Five of the 2,112 normal mature babies succumbed, a rate of 0.24 per cent, which in this series represents the hazard to a normal term baby of being delivered by section.

The lower segment operation was used in 96 per cent of the elective sections. Spinal anesthesia was used in 94 per cent. Morbidity was 8.4 per cent. Antibiotics were used prophylactically in 24 per cent of the cases in the second period, as compared to 46 per cent in the first period. Correspondingly, the administration of blood transfusions dropped from 25 to 14 per cent. There were no maternal deaths in elective section.

Appendectomy

Incidental appendectomy was performed at the time of cesarean section in 193 cases. No obvious postoperative complications commonly developed. The morbidity rate was 8 per cent. None of the patients died.

Age and section

A few interesting facts were discovered concerning sections at the extremes of reproductive life (Table XII).

The greater incidence of morbidity and fetal loss in the younger group may be a reflection of the hesitancy to perform section on such young girls.

Sterilization

One or more previous sections is the chief indication for sterilization in Cincinnati. The

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Table XII. Cesarean sections in young and old patients

17 years and younger		40 years and older	
Age at delivery	No. cases	Age at delivery	No. cases
17	77	40	113
16	49	41	79
15	20	42	49
14	9	43	38
13	3	44	26
		45	12
		46	5
		47	3
		48	1
	-	49	1
Total	158 (160 babies)		327 (329 babies)
Nulliparas	80%		25%
Morbidity	44%		10%
Previous section	22%		34%
Youngest multipara	15 years		
Oldest nullipara		49 years	
Fetal loss	13%		7.6%
Indications for primary se	ections		
Disproportion and			
malpresentation	50%		34%
Bleeding	17%		29%
Functional	19%		11%
Maternal mortality	0		2 (0.6%)

procedure is permitted in 6 of the 9 hospitals. The Pomeroy and Irving methods are the ones commonly employed. As shown in Table XIII there is decreasing tendency to sterilize patients because of uterine section scars. The decrease in sterilizations is obvious. The probable explanation is the recognition that section is becoming safer, and that patients desire larger families. A possible factor is the increasing number of patients who for religious or other reasons are opposed to sterilization.

Table XIII. Tubal ligation (sterilization) at time of section

At which section	% of patients sterilized	
sterilized	1950-1954	1955-1959
First	7.7	4.7
Second	29	12
Third	61	50
Fourth	47	44
Fifth	75	60
Sixth		50
Gross per cent of patients sterilized	19	13

Comment

Innumerable fascinating discoveries were made in the review of these cases. One patient underwent section 24 days after "thorough" curettement. In 2 cases the diagnosis of pregnancy was made, at the time of intramural myomectomy, by aspiration of amniotic fluid. Both pregnancies continued to term. In one case a patient was delivered of a dead twin vaginally, then a live twin by cesarean section an hour or so later. In 2 cases where the tubes had been surgically implanted in the uterine wall, 1 to 3 cm. defects in the myometrium adjacent to the tubes were found at the time of elective section. In one patient with a large hydrocephalic baby in breech presentation, it was discovered at the time of section that the head could not safely be delivered through the uterine incision, so cranial centesis was performed. The baby survived.

In my community, at least, I believe cesarean section could safely be resorted to more often. Section should not be considered an admission of obstetrical failure, but rather a method of delivery to be used without

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qualm when a complication is present which threatens the life or health of mother or bally and when experience (that is, statistics) show that cesarean section is the best method of delivery.

The demonstration that, for the baby, elective repeat section is safer than awaiting labor or other emergency (including rupture of the uterus) suggests to me that the solution to the problem of determining the maturity of the unborn baby will save more babies than will abandonment of elective repeat section.

Three patients in this series had invasive carcinoma of the cervix. Assuming that all patients with known carcinoma of the cervix were delivered by cesarean section, this incidence of 3 cases in 220,000 deliveries seems remarkably low. It is hoped that no cases were overlooked, or that, if present, the cancer was discovered early in pregnancy and was treated adequately before the babies reached a weight of 500 grams.

Morbidity figures demonstrated the fallacy of blind acceptance of routine treatment advocated by others. It is clear in our community that in some hospitals the prophylactic use of antibiotics in elective cases is unnecessary, in others it is advantageous. In the majority of cases with morbidity the temperature was 101° F. or less and was present on only 2 days. This raises the question of whether morbidity as currently defined has any real significance today. None was evident in this series. Perhaps the whole problem of morbidity in obstetrics should be re-examined.

Too many mothers still die following cesarean section as well as following vaginal delivery. Maternal deaths ordinarily fall rather clearly into one of three categories: (1) shose due to causes unrelated to pregnancy; (2) those due to pregnancy but unrelated to the method of delivery; and (3) those directly related to the method of delivery. It appears to me that most of the deaths in this series fall into Categories 1 and 2. The glaring exception is the group of deaths due to embolism. We must find a way to prevent embolism after cesarean section.

The common objections to performing cesarean section are immediate danger to the patient from anesthesia, hemorrhage, and infection, the danger of embolism, the potential limitation of family size, and the danger of rupture of the uterus in future pregnancies. Except for embolism, I believe most of the dangers have been overemphasized. As far as I know, there has not been a single maternal death due to rupture of a cesarean section scar in Cincinnati in the last 10 years. The prevention, early recognition, and early treatment of hemorrhage should reduce the number of deaths due to hemorrhage, shock, and renal failure.

More than 1 per cent of patients who had had previous cesarean sections had placenta previa in a subsequent pregnancy. The same was true of premature separation of the placenta. These, with an appreciable percentage of patients with bleeding not otherwise defined brought to over 3 per cent the number of patients with previous sections who developed significant bleeding in the latter half of a subsequent pregnancy. Only 0.4 per cent of patients not having previous sections had similar bleeding. Even discounting the possible tendency to perform cesarean section more readily on a patient who previously had had a section and is bleeding, it appears that cesarean section predisposes to significant bleeding in the second half of subsequent pregnancies. The explanation for this is not known.

Fetal salvage of babies weighing less than 1,000 grams was so low—only 2 of 27—following delivery by section that serious doubt is raised as to the merits of section when the baby is in this weight category.

Opponents of the free use of cesarean section demand that increase in the use of section, to be justified, must result in "a dramatic reduction in perinatal mortality. In this series, however, 22 babies had to be saved to cause a shift of one one-hundredth of a percentage point in the city-wide perinatal loss rate. Saving one baby by section causes the section rate to increase 35 times as much as it lowers the total perinatal loss rate. To those interested chiefly in rules

and regulations, this seems disproportionate; to those of us interested in the welfare of mothers and babies, the risk, if any, is justified.

While not totally opposed to rigid criteria and hard-and-fast rules, it seems to me there are a significant number of women who have a multiplicity of minor abnormalities the combination of which make section seem advisable but no one of which alone justifies the operation. For instance: A 29-year-old primigravida has been married 10 years and has not previously conceived. She is 19 days past the estimated due date. The membranes rupture spontaneously, and the amniotic fluid is noted to be brownish green. The head is presenting at station minus-3. X-ray examination leaves doubt as to whether there is adequate room. The fetal heart tones are normal. The cervix is 75 per cent effaced but only 1 cm. dilated and is rigid. Contractions are good when they occur, but they are irregular—every 4 to 8 minutes. Dilatation increases to 7 cm. in 12 hours, but remains the same for the next 3 hours. What shall be done? Oxytocin drip? There is a question of disproportion. Section? What would the diagnosis be? Elderly nullipara? No, the patient is only 29. Disproportion? Not proved. Postmaturity? Uncertain. Fetal distress? The heart tones are good. Inertia or dyskinesia? Progress has been made. Cervical dystocia? Denied by many. But the outlook for the baby is not favorable if vaginal delivery is awaited. I would perform cesarean section without hesitancy, with no really acceptable preoperative diagnosis.

I believe the 0.24 per cent neonatal loss of term-sized babies delivered by elective section is perhaps significant, for it represents the minimum loss rate we have achieved under today's best circumstances. Improvement can probably be made, but it will be slow.

Delivery of a known dead baby by cesarean section after vigorous attempts at vaginal delivery was performed a few times. I believe that craniotomy, as gruesome as it is but followed by vaginal delivery, might have been justified. On the other hand, I should

like to see version-and-extraction, difficult midforceps delivery, the Thorne maneuver, difficult breech extraction, and induction of labor (except under the most ideal circumstances) relegated to that limbo occupied by high forceps.

To me cesarean section is the proved answer to most of the dangerous complications of late pregnancy, labor, and delivery.

Summary

- 1. All of the cesarean sections—6,265—performed in Cincinnati, Ohio, in the 10 year period 1950-1959 are reviewed.
- 2. Twenty-three mothers died within one year of cesarean section. No mortality rate on this or any other basis is calculated.
- 3. The gross perinatal loss rate was 7.6 per cent.
- 4. The results of cesarean section in transverse lie are reported and compared with the results in similar cases of vaginal delivery in Buffalo.
- 5. The results in cesarean section for premature separation of the placenta are presented and are compared with those in similar cases of patients delivered vaginally in Atlanta.
- 6. The fetal and maternal results in diabetes, prolapse of the cord, repeat sections, elective sections, and sections at the extremes of reproductive life are given.
- 7. Perinatal mortality figures in elective and emergency repeat sections are compared. Elective repeat section appears to have the lesser perinatal loss rate.
- 8. The hazard of neonatal death of a normal term-sized baby delivered by elective section proved to be 0.24 per cent in our community.
- 9. A downward trend is noted in sterilization.
- 10. A plea is entered for the establishment of an acceptable classification category for cases with a multiplicity of borderline indications for section.
- 11. Serious complications were rare The majority are discussed.
- 12. Brief consideration is given to morbidity and the use of antibiotics. Morbidity

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among Negro women was found to be higher than among white patients. The significance of morbidity is questioned.

- 13. Incidental appendectomy in 193 cases is discussed.
- 14. A possible increase in bleeding complications of late pregnancy in patients with section scars was noted.
- 15. It is concluded that cesarean section is the best method of delivery in the majority of cases where there is real or potential threat to the life or health of either mother or baby, or both.

Addendum. Since these statistics were compiled, one more patient died, of inflammatory carcinoma of the breast.

I wish to express my deep gratitude to the record room personnel of Bethesda, Christ, Deaconess, Catherine Booth, Good Samaritan, Jewish, General, St. Mary, and Our Lady of Mercy Hospitals. Without their cheerful, unflagging, and efficient help this study would not have been possible.

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Discussion

Dr. H. Close Hesseltine, Chicago, Illinois. Potter found a mortality rate of only 0.5 per cent in all live, term births, without correction. Freese and Hesseltine noted that the mortality for babies born by cesarean section, in the elective or other categories in which there was absence of fetal embarrassment and complications, mounted to 0.9 per cent.

If one depends on the spontaneous onset of labor to determine when term is reached, one encounters frequently situations unfavorable for the operative procedure, such as a recent meal, an unemptied lower bowel, irregular hours, competition for an operating room, and complications like upper respiratory infection, acute gastroenteritis, and other conditions. The elective planning for cesarean section permits the best possible preparation of the patient, emotionally and physically.

There are, however, proponents of the view that some labor has beneficial effects upon the unborn. Presumably, there are minor shifts of some fetal body fluids (for instance, cerebrospinal).

The data on the use of antibiotics for "prophylactic purpose" in the different hospitals permit various interpretations. At the Chicago Lying-in Hospital, antibiotics are used on direct indication with but few exceptions. All authorities on antibiotics agree that, when these drugs are employed, dosage and duration of therapy must be

adequate and that proper selections are demanded. The term "broad coverage" is a misnomer. Most of the antibiotics have certain breadth but also definite limitations.

Comments on the route of administration of antibiotics may be offered. Unless patients are on a full or general diet, antibiotics by mouth cause changes in the gastrointestinal flora and also intolerance. Penicillin, generally, should not be given orally. Not only will a change in bowel flora contribute to diarrhea and staphylococcic infection, but may prevent the normal production of vitamin K.

Current concepts of morbidity need reconsideration. The old standard to establish the diagnosis of febrile course of 100.4° F. on two consecutive days, excluding the first, seems out of character by present-day standards. We believe that D'Esopo's proposed standard, using 99.7° as the dividing line for fever and the sums of the tenths of degrees, was realistic.

A point for criticism in this presentation relates to the matter of routine or free use of x-ray photography. The recently determined facts about the potentially injurious effect of x-rays upon the young fetus and fetal gonads give cause for restraint and caution in the use of radiological methods.

On first consideration, one may be inclined to offer commendation for the infrequent use of cesarean section for "breech." Yet today there

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is a tragically high fetal mortality and morbidity in association with vaginal delivery with the breech as the presenting part. The incidence of breech deliveries is only 3 per cent, but fetal loss and damage are 4 to 10 times greater than the average for all deliveries. At the Chicago Lying-in Hospital, we are increasingly resorting to cesarean section for delivery for breech presentation. Cesarean section should be used more often in judiciously selected patients when the breech is the presenting part. The indication should be related to the estimated fetal size and the pelvic capacity.

Local anesthesia is the safest for mother and fetus, but it has limitations and inadequacies. In the absence of contraindications, spinal anesthesia offers a good margin to the unborn and also offers adequate anesthesia. Nevertheless, there are indications and need for general anesthesia. Premedication may be most undesirable for the fetus.

DR. RALPH A. REIS, Chicago, Illinois. Dr. Barter's paper disappointed me, because a discusser and I found Dr. Barter does everything exactly the way we do. The only place we differ, is that after the baby's head has been delivered we relax. Then we let the anesthesiologist give the mother intravenous ergonovine and wait for the responding uterine contractions to expel the baby's torso. This compresses the chest thoroughly and causes fluid to run out of the nostrils and out of the mouth! We have thus done away with the need for lavage, even in the term babies of diabetic mothers.

The technique described has worked out very well for us. Our time in delivering the baby's head through the incision is 5 minutes. It takes another 4 minutes to finish the delivery. We think this is the reason we have not been plague 1 by hyaline membrane disease of the newborn in our cesarean section babies.

Another point I want to emphasize is avoidance of the shibboleth of prematurity in repetit elective cesarean section. This stems from the habit of scheduling the operation 10 to 14 days before the patient's estimated date of confinement. We have for years scheduled operation 24 to 48 hours after the estimated date of confinement and, while this will once in 20 times get us up at night, it has done away to a large extent with the problem of prematurity in repeat cesarean section babies.

Dr. Bryant (Closing). Every once in a while something good is advocated by a particular person which when used generally by men with little experience does not work out well. The classic example of this was the use of version and extraction as a routine procedure. Dr. Potter got magnificent results but it was soon proved that the procedure could not readily be adopted by the average practitioner of obstetrics. Any procedure as popular as cesarean section should be studied on a community or broad basis to determine its adaptability to general use.

I would like to decry the common practice of comparing or contrasting the results following cesarean section with the results following normal vaginal delivery. About the only real conclusion that can be reached from such a comparison or contrast is that people who are sick are sicker than people who are not sick. Truly significant conclusions can be drawn only if comparisons are made between comparable cases. It is almost impossible to do this today in any one clinic.

Cesarean section anesthesia

ROBERT H. BARTER, M.D.
SEYMOUR ALPERT, M.D.
TAYLOR H. KIRBY, M.D.*
CHARLES M. TYNDAL, M.D.
Washington, D. C.

CESAREAN section anesthesia continues to have a major role in obstetric practice.¹⁻⁴ Each of the many anesthetic agents which has been used since the advent of abdominal delivery has had its advantages and its disadvantages. The apparent advantage of each new drug ultimately has been offset by its undesirable side effects.

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The difficulty of finding a suitable anesthetic agent is complicated by the fact that the perfect drug for this operation must provide a safe and pleasant anesthetic for the mother with no deleterious effect upon the unborn fetus. The ideal agent should be universally adaptable for both the elective and the emergency types of the operation. Good obstetric anesthesia requires a maximum of coordinated effort between the anesthesiologist and the obstetrician. The teamwork which is the inevitable sequel of such a cooperative effort provides the most satisfactory anesthesia and the best obstetric results.

The cesarean section problem is one of increasing magnitude because of (1) the rising birth rate and (2) the higher incidence in many hospitals of the primary type of operation. This combination, plus the

larger number of patients each year who have repeat sections, is increasing the total number of cesarean sections done annually.

Cesarean section, in the majority of instances, is an emergency with the patient likely to be a poor risk for any form of anesthesia. The presence of maternal hemorrhage, premature labor, toxemia, previous exhaustive labor, and underlying medical or surgical diseases all contribute to the complexity of the anesthetic problem. Recent ingestion of food by the patient who is to have an emergency cesarean section creates a serious hazard. There are few other examples of a patient's being in such temporary but dire danger from an anesthetic standpoint.

Regional anesthesia is the type generally advocated for cesarean section in many institutions^{7, 8} as well as in the standard textbooks^{9, 10} of obstetrics. Local anesthesia or some forms of spinal anesthesia, however, despite their more or less general acceptance, have many disadvantages and some inherent dangers.¹¹ By contrast, this series of 1,563 patients, more than 90 per cent of whom were delivered under a balanced technique of intravenous and inhalation anesthesia, is deemed worthy of presentation because of the favorable results obtained for both mothers and infants.

Material and results

From Jan. 1, 1953, through Dec. 31, 1959, 1,563 cesarean sections were performed at The George Washington University Hospital. During the same interval there

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Presented at the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960.

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were 25,690 births. The cesarean section rate for the 7 year period was 6.08 per cent. There has been a small but definite increase in the number of cesarean sections performed each year, ranging from 4.75 per cent in 1953 to 7.5 per cent in 1959 (Fig. 1). The average age of the patients was 31 years. The average gravidity of the patients was 2.45, the average parity of the patients 1.01. The largest baby delivered in this series weighed 5,358 grams. The average weight of the delivered babies was 3,175 grams. Two hundred and fourteen patients or 13.9 per cent had antepartum bleeding of varying degree prior to the operative intervention.

Six hundred and sixty or 42.2 per cent of the patients were in labor at the time of the cesarean section. One thousand four hundred and eight or 90 per cent of the sections performed were of the low cervical type. There were 80 classical sections, 50 extraperitoneal sections, and 25 cesarean hysterectomies.

Of the 1,563 cesarean sections, 1,441 or 92.2 per cent were done under combined intravenous and inhalation anesthesia. Conduction anesthesia was used in only 122 patients or 7.8 per cent of the total. The

latter was used principally (1) when the patient preferred to be awake during the operation, (2) when the fetus was extremely small, and (3) for the teaching of conduction anesthesia when specifically indicated,

There was no maternal mortality in this group of 1,563 patients.

As most of the sections were done with the combined type of anesthesia a significant fact was the average time from the start of anesthesia to the delivery of the fetus. That ranged from an average of 12 minutes, 37 seconds in 1953 to 7 minutes, 40 seconds in 1959, demonstrating a substantial decrease in the operating time necessary for the delivery of the infant (Fig. 2).

Approximately 75 per cent of the babies were delivered in less than 10 minutes from the start of the anesthesia (Fig. 3).

In this compilation the average time for spontaneous respiration to occur from the time of delivery was 1 minute, 42 seconds. More than half of the infants breathed spontaneously. If there was a delay in the onset of spontaneous respirations, all of the infants received manually regulated intermittent positive pressure oxygenation with the Kreiselman infant resuscitator. An average inspiratory pressure of 12 mm. Hg was

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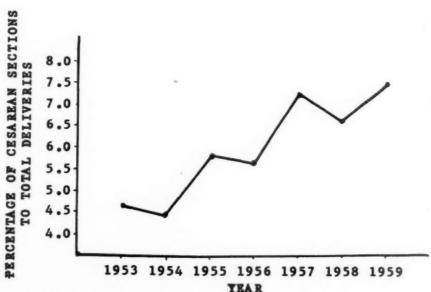


Fig. 1. Incidence of cesarean sections.

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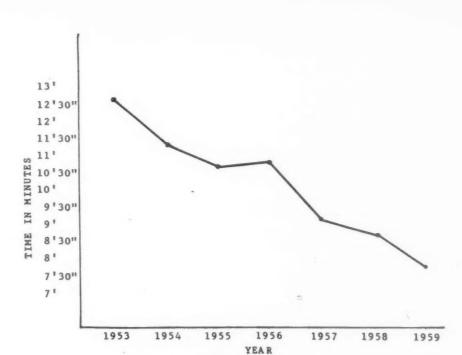


Fig. 2. Minutes from induction to delivery.

employed. In almost every infant in whom more than 2 minutes elapsed before spontaneous breathing began, there was no cause for concern as the infants were well oxygenated. Aspiration of the stomach, as advocated by others, 12 was done routinely.

Six hundred and eighty-seven or 43.9 per cent of the cesarean sections were elective in type. Six hundred and fifty-one or 94.7 per cent of the infants from the elective group weighed more than 2,500 grams. Of that group 645 or 99 per cent of the babies survived with only 6 or 1 per cent of the babies failing to survive. In the elective group 41 or 5.9 per cent of the babies were premature. Twenty-seven or 66 per cent of those infants survived while 14 or 34 per cent of the babies died. The uncorrected fetal mortality for the entire elective group was 2.9 per cent.

In the entire group of 1,563 cesarean sections there were 29 stillbirths. Most of the stillbirths were the result of premature separation of the placenta, diabetes in the mother, severe erythroblastosis, or developmental anomalies in the infant incompatible

with life. Two of the stillbirths were the result of rupture of the uterus.

Of the 29 stillbirths the cause of death in none could be attributed directly to the anesthesia.

There were 52 neonatal deaths in the entire series with only 14 of those being in term infants. Of the 14 term infants 4 had congenital anomalies and one had severe erythroblastosis. The remaining 38 infants in this neonatal mortality group were pre-

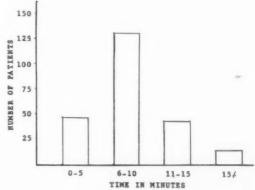


Fig. 3. Minutes from induction to delivery in 1959.

mature infants. Five of the 38 were anomalous. Hyaline membrane disease accounted for at least 8 of the deaths in this group. Of the remaining 25 premature infants, prematurity as such was given as the cause of death. The uncorrected perinatal mortality for the entire series was 5.12 per cent. The corrected perinatal mortality for the entire compilation was 0.89 per cent.

An inquiry based upon random selection was directed to the various pediatricians who cared for the babies following delivery. Over 500 or approximately one third of the infants in this study were included in the follow-up. No instance of retarded development or any other late complication was reported.

Method

The patients who had been in labor, in almost all instances, had been given meperidine hydrochloride (Demerol), 100 to 200 mg., as well as intravenous sodium pentobarbital (Nembutal) in doses ranging from 200 to 350 mg.

In recent years, no premedication has been given to the patients scheduled for elective cesarean section prior to the induction with thiopental sodium (Pentothal sodium), thus helping to reduce any depressant effects upon the fetus.

The method by which these patients had abdominal deliveries is as follows:

The medical anesthesiologist described to the patient the details of the combined technique of intravenous and inhalation anesthesia. Preferably this is done in the presence of the obstetrician. The patient is told that all surgical preparation of the operative site and the preoperative draping is to be done while she is awake so that only a minimal amount of the anesthetic agent will be transmitted to the fetus.

Each step of the preparation and draping is explained to the patient as it is performed. A 19 gauge 1½ inch needle is inserted in an antecubital vein. A slow drip of 5 per cent dextrose and water is started via a three-way stopcock. A 20 c.c. syringe containing 2½ per cent thiopental is at-

tached to the second outlet of the three-way stopcock. After the patient has been draped and with the surgeon and his assistants ready an average dose of 250 mg. of thispental is rapidly administered. In approximately 30 seconds the eyelid reflex is lot. As the patient becomes drowsy, a mixture of 75 per cent ethylene and 25 per cent oxygen is administered to the patient by means of a mask. The incision can usually be made 60 to 90 seconds after the start of the induction. The patient may move slightly as the incision is made, in which case an additional 50 to 100 mg. of thiopental is administered. Signs of light anesthesia such phonation or rapid respirations are treated with additional doses of thiopental. The average dose of thiopental injected for the delivery of the fetus is 350 mg.

In less than 10 per cent of the patients a muscle relaxant such as decamethonium bromide (Syncurine) or succinylcholine chloride (Anectine) is given intravenously in small doses.

Nasopharyngeal and oropharyngeal airways are utilized only when necessary to correct difficulties in respiration. A cuffed endotracheal tube is inserted immediately before operation in any patient who has given a history of recent food ingestion.

The anesthesia was administered to each patient in this series by a physician anesthesiologist on the staff of the University Hospital.

There were only 19 anesthesia complications in the group of 1,441 patients who received general anesthesia. The most important complication was that of 8 instances of vomiting. Aspiration of emesis occurred 3 times. The other complications were not serious. There was no persistent anesthetic morbidity. Three of the 122 patients who had spinal anesthesia had persistent spinal headaches. Maternal morbidity of relatively minor degree was present in 181 patients.

Comment

A balanced technique combining introvenous and inhalation therapy has been found to be a most satisfactory type of anesthesia sa control of the man incident them.

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for cesarean sections. The operation of cesa ean section, performed as an emergency more frequently than as an elective procedure, puts a premium on excellent anesthesia and superior surgical technique, as maternal mortality and morbidity is usually increased in cesarean section delivery. 6, 13 In this series of patients there was no maternal mortality.

Although the hazard of maternal mortality is a constant threat with each cesarean section, the problem of neonatal morbidity and mortality is the greatest problem in abdominal delivery. In each series reported the figure for perinatal mortality is greater than that for vaginal delivery.^{2, 14} As stated, however, cesarean section is done in many instances for a maternal complication which necessitates abdominal delivery to save the life of the mother. Under those circumstances the fate of the baby assumes secondary importance. The corrected perinatal mortality was less than 1 per cent, a very reasonable figure.

In the elective cesarean section group only 6 babies out of 651 weighing more than 2,500 grams failed to survive, giving a perinatal mortality of only 1 per cent. However, in the same elective group when the infant weighed less than 2,500 grams 14 of 41, or 34 per cent of those babies, failed to survive.

Prematurity as such continues to be the leading cause of all perinatal mortality. It is an even greater factor in cesarean section. Hyaline membrane disease, which caused a fairly large portion of the neonatal deaths in this series, is found principally in premature infants. ¹⁴ Its incidence is probably increased by compounding the effects of cesarean section upon those of prematurity. ¹⁵ Experimentally, however, delivery by hysterotomy did not result in an increase in hyaline membrane disease. ¹⁶

A constant concern in elective cesarean sections is the unintentionally high incidence of premature infants. It varies from 3.8 to 13.8 per cent.^{6, 7} In this series of elective cesarean sections nearly 6 per cent of the babies were delivered prematurely. Because of the inexorable increase in peri-

natal mortality when a baby is born prematurely by cesarean section every effort should be made to prevent the "too early" cesarean section.

The practice of allowing all patients for repeat or elective cesarean sections to go into labor prior to the operative delivery has its greatest advantage in relieving the obstetrician of the decision for setting the time of delivery. It decreases the incidence of prematurity to some extent, but it by no means eliminates it. It has the disadvantage of making the cesarean section no longer an elective procedure. The advantage of having the patient well prepared and in optimum condition for operation is lost. From an anesthetic standpoint, at least, the dictum of "once a section, always a section" has many merits. From the pediatric point of view, however, there is less reason for one to be so rigid concerning its application.

The advantages of the balanced type of anesthesia described above for cesarean section are many: (1) this type of anesthesia is the most universally available; (2) it is generally easier to employ; (3) it is less time-consuming; (4) there is less morbidity; (5) it is the type of anesthesia mandatory in most emergency sections; (6) there is usually no precipitous fall in the maternal blood pressure with its calamitous effect upon the fetus; (7) it is not irreversible in its effect; and (8) it is usually more pleasant for the patient. Concerning the last point, the use of local or spinal anesthesia for abdominal delivery is regarded unfavorably by many patients in the area served by this hospital.¹⁷ Furthermore, many patients prefer not to be awake during any surgical procedure. No one should be forced to accept an anesthetic agent which is incompatible with the equanimity of that individual. An additional factor is the greater incidence of medicolegal problems as a result of mishaps with conduction anesthesia.18 If balanced anesthesia has greater patient appeal and if the effects upon the fetus are negligible, then there would seem to be little need for other forms of anesthesia.

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The undeniable disadvantage of the intravenous and inhalation technique is the fetal depression induced by the drugs administered to the mother, although there is evidence that the latter fact has been given too much credence. With positive pressure oxygenation available immediately upon delivery, the factor of fetal depression assumes minimal importance. The many advantages of the intravenous and inhalation techniques more than offset the minor disadvantage of temporarily delayed spontaneous respirations in a well-oxygenated infant.

Any anesthesia for abdominal delivery which uses a depressant drug does put a premium on surgical skill and dexterity. The time from the induction with the anesthetic agent or agents to the delivery of the baby is important with this technique. However, it is perhaps no more important here than with forceps or breech deliveries when inhalation anesthesia is used.5 Undeniably, the smaller the amount of depressant drug which the fetus receives, the more alert will be the baby. In this series, the time from induction of the anesthetic to the delivery of the baby has been reduced by almost half in a 7 year period (Fig. 2). The average time for delivery of the baby in 1959 was 7 minutes and 40 seconds. This interval is probably too brief for the fetus to receive enough of the anesthetic agent to be of great significance.

A large percentage of the patients had had some type of previous abdominal operation. Repeat cesarean sections were done in 630 or 40.3 per cent of the patients. Although patients who have had a previous section may require a slightly longer time for delivery than do patients having primary sections, the time factor does not have to be too much longer.

Summary

- 1. A series of 1,563 cesarean sections h. s been presented.
- 2. Ninety-two per cent of the patients were delivered under a balanced type of anesthesia utilizing a combination of intravenous and inhalation techniques.
- 3. This technique was generally acceptable to the patients as opposed to a large number of patients who are fearful of spinal and other forms of regional anesthesia.
- 4. There was no maternal mortality in this series.
- 5. The uncorrected perinatal mortality was as low in this series as in those reported by others.⁶
- 6. The corrected perinatal mortality was less than 1 per cent.

Conclusions

- 1. Prematurity continues to be the leading cause of perinatal mortality in abdominal deliveries.
- 2. The greatest hazard of elective cesarean section is the delivery of a premature infant
- 3. Hyaline membrane disease, a factor of tremendous importance in infants delivered by cesarean section, is an unsolved enigma
- 4. Excellent anesthesia is in general due to the skill of the anesthesiologist, regardless of the agent employed.
- 5. The balanced technique anesthesia requires perfect teamwork.
- 6. A combination of above average obstetrical judgment, intelligently administered anesthesia, and skillful surgical technique will continue to give the best results in delivery by cesarean section.

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Dr. WOODARD D. BEACHAM, New Orleans, Louisiana. During the 11 years ending June 30, 1960, at the New Orleans Charity Hospital there were 129,447 deliveries with 5,266 cesarean sections (Table I). Charity Hospital Anesthesiology Chief John Adriani states that there has not been a death in the "spinal-anesthesia-for-cesarean" series since 1942. During the past decade over 85 per cent of the patients undergoing cesarean section in that institution have been given the benefit of intrathecal analgesia. Relatively few of the patients have had local infiltration anesthesia. Cyclopropane is the preferred agent for inhalation anesthesia because it is readily effective, permits a high oxygen concentration, and is rapidly eliminated. Pentothal sodium administered intravenously to the mother rapidly reaches the fetus, and Adriani states that the concentration in the blood of the mother and of the fetus is essentially the same within 3 minutes after injection.

Table I. Charity Hospital at New Orleans

	Cesarean sections	Deliveries
1949-1950	344	10,549
1950-1951	396	11,189
1951-1952	350	11,093
1952-1953	395	11,466
1953-1954	481	11,584
1954-1955	576	12,568
1955-1956	618	12,782
1956-1957	531	12,796
1957-1958	567	12,727
1958-1959	529	11,900
1959-1960	479	10,793
Total	5,266	129,447

Since 1945, at the Southern Baptist Hospital in New Orleans, spinal anesthesia for cesarean

section has gained steadily in popularity. Of the 2,672 cesarean sections performed in the 9½ years beginning Jan. 1, 1951, 2,499 were done with patients so anesthetized (Table II). One hundred and sixty-three had inhalation anesthesia and 12 patients had local infiltration anesthesia. Anesthesiologist Frank Leo Faust declares, "Properly administered differential spinal anesthesia offers sensory and motor anesthesia with a degree of safety to baby and mother second to none for operations below the tenth thoracic dermatome."

The advantages to the obstetrician of operating upon patients under spinal anesthesia are well known. As the result of not being rushed by the clock he can prevent blood loss, avoid injuries in cases complicated by adhesions, choose his uterine incision, and he can usually maintain the integrity of the amnion until the head is ready to be delivered in cases of cephalic presentation. By keeping the amnion intact until the fetal head has been at least partially delivered, we have prevented babies from aspirating blood and, consequently, certain problems have been obviated. These fortunate babies are born with a caul. For the baby spinal anesthesia offers a high concentration of oxygen and no anesthetic agents in the maternal blood stream to affect the infant adversely. The mother has the advantage of being able to clear the upper digestive and respiratory tracts under her own power.

To guarantee safety for the baby and the mother, two systems must be supported, namely, the respiratory and the circulatory systems. The respiratory system is protected by keeping the motor level of anesthesia below the eighth thoracic segment. This is done by regulating the specific gravity of the anesthetic agent, the volume of the solution to be injected, the position of the operating table, and the time of administration with reference to the uterine contractions.

Table II. Anesthesia for cesarean sections at Southern Baptist Hospital

	1951-1954	1955	1956	1957	1958	1959	Half of 1960	Total
	1931-1934	1955	1930	1937	1930	1939	1900	1 otat
No. of cases	998	261	306	348	326	294	139	2,672
Spinal	928	253	282	331	304	276	123	2,499
Inhalation	63	8	23	15	21	18	15	163
Local	7		1	2	1		1	12

Obviously, the height, weight, and physique of the patient are duly considered. The circulatory system is protected and/or maintained by preoperative administration of ephedrine sulfate and intravenous fluids. Vasopressors are given if needed to take care of reflexes during the operation. Blood is used for purposes of replacement of excessive blood loss as in cases of placenta previa but in most of our cases in private practice transfusion has not been required. Diseases of the central nervous system, dermatologic conditions overlying the lumbar spine, and decreased blood volume and anemia due to hemorrhage are contraindications to spinal anesthesia. In the presence of shock due to hemorrhage under emergency conditions, we prefer intravenously administered scopolamine as premedication for cyclopropane anesthesia and a trace of ether to reduce cardiac sensitivity and permit rapid clo-

Dr. J. Bay Jacobs, Washington, D. C. If labor starts spontaneously 2 or 3 weeks before term the fetus stands a better chance of surviving than if labor is induced or a cesarean section

performed the same number of weeks before term. There are many ways of determining prematurity. Careful attention should be paid to the estimated date of confinement even though it is often inaccurate. Then, of course, past history, the size of the previous babies, the height of the fundus, the relative amount of amniotic fluid, whether or not the presenting part is engaged, and, by vaginal examination, the character of the cervix should be taken into consideration. A single lateral pelvic roentgenogram taken in the standing position gives in about two thirds of the cases a very excellent view of the biparietal diameter. With reservations with respect to the size of the husband's head, if the biparietal diameter measures 91/4 cm., the fetus should be just about mature.

I think that Dr. Barter's reported incidence of a little over 7 per cent of cesarean sections is relatively high. At Arlington Hospital we have an incidence, I should say, of about 2½ per cent, including repeat sections, and I think we get very good results so far as the fetal outcome is concerned.

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Vaginal delivery after cesarean section

H. L. RIVA, COLONEL, MC, USA
JOHN C. TEICH, CAPTAIN, MC, USA
Washington, D. C.

THIS is a continued report of a study of vaginal delivery after cesarean section. All patients were attended by a closed staff under the direction of the senior author and his assistant, who evaluated each patient prenatally and during labor and delivery.

Several factors encouraged this study; first, successful reports by experienced clinicians in obstetrics and gynecology; second, evaluation of a series of extraperitoneal cesarean sections shortly after World War II; and, third, the facilities of this hospital afforded the opportunity to make this study.

Patients previously scheduled for repeat cesarean section were permitted to go into labor in order to develop an adequate lower uterine segment. On vaginal examination prior to section, labor was found to be progressing rapidly in many and it was questionable whether or not cesarean section could be accomplished before vaginal delivery occurred. Examination of the uterus following delivery revealed few uterine defect from previous section. Since this hospital afforded facilities such as operating room, blood bank, personnel trained in intra-arterial transfusion, and an anesthesiology service available 24 hours a day, it was felt that this study could be undertaken here.

> From the Obstetrical-Gynecological Service, Walter Reed General Hospital, Walter Reed Army Medical Center. Presented at the Seventy-first Annual

> Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960.

The study

All patients in this series were followed in a special clinic. Emphasis was placed on evaluation of all data on previous deliveries. Careful evaluation of each patient was made every 2 weeks until 28 weeks of gestation, with sterile vaginal evaluation at weekly intervals thereafter. X-ray pelvimetry and placentography from previous pregnancies and the present pregnancy were compared. Patients were admitted 10 to 14 days prior to the estimated date of confinement.

Each patient was followed in labor in the operating room, with vaginal and abdominal operative setup available. In most, vaginal delivery, when accomplished, was performed shortly after termination of the first stage of labor, with use of outlet forceps and mild analgesia, trichlorethylene and lidocaine pudendal block. Exploration of the uterus after delivery was routine to determine placental site and to detect any possible defect from the previous section.

Cesarean section rates and special groups

Pertinent general statistics before and after initiation of this study are indicated in Table I.

The cesarean section rate dropped from 2.93 per cent to 1.54 per cent. Of the 214 consecutive patients in this series, 73.8 per cent were delivered vaginally (Table II).

Repeat cesarean sections represented 50 per cent of the total sections performed in this clinic when the dictum "once a section, always a section," was being followed. It is

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Table I. Analysis of deliveries and results for period prior to and during this study

	January, 1948, to January, 1953	January, 1953, to July, 1960
No. deliveries	6,874	12,424
No. sections	202	192
Section rate	2.93%	1.54%
No. previous cesarean sections	101 (50%)	214 (61.2%)
No. repeat cesarean sections	98 (97%)	56 (26.34%)
Fetal mortality rate (uncorrected)	3.2%	2.9%
Maternal deaths	3 (uncorrected)	6 (uncorrected

Table II. Previous cesarean sections (214 cases)

Method of delivery	No.	Per
I. Vaginal delivery	158	73.8
A. Method of delivery	130	70.0
1. Spontaneous	29	18.4
2. Low forceps	121	76.6
3. Midforceps	4	2.5
4. Breech	4	2.5
II. Repeat cesarean section	56	26.2
A. Type of section:		
1. Extraperitoneal	36	64.3
2. Low cervical	12	24.4
3. Classical	4	7.1
4. Total cesarean hyster-		
ectomy	2	3.6
Subtotal cesarean hyster- ectomy	2	3.6

Table III. Indication for the first section in previous cesarean section cases

Indication	No. cases	Per
Cephalopelvic disproportion Third trimester bleeding	83	39.2
(abruptio and previa)	61	28.5
Abnormal presentation	- 20	9.3
Inertia	10	4.6
Pre-eclampsia-eclampsia	9	4.2
Miscellaneous	31	14.2
Total	214	100

said that when the cesarean rate is low, the clinic repeat section incidence is also low. The repeat cesarean rate would have increased to 61.2 per cent if all of these patients had had cesarean section. The fetal and maternal mortality figures were not significantly altered by this study.

In 214 cases the indication for the first cesarean section was cephalopelvic disproportion in 39.2 per cent and abruptio previa in 28.5 per cent (Table III), or two thirds of the reasons for the initial section.

Pelvimetry studies in patients in whom the original section was for cephalopelvic disproportion. Of those patients (49) who were subsequently delivered vaginally, only 10 per cent had a Mengert capacity index of the inlet and midpelvis below 85 per cent (Tables IV and V). However, of those patients who required a repeat section (34), 50 per cent had a Mengert capacity index of the inlet and midpelvis below 85 per cent. It is our contention that cephalopelvic disproportion cannot be properly assessed without a trial of labor with ruptured membranes.

Comparison of infant weights in patients with cephalopelvic disproportion delivering vaginally. Infants delivered vaginally weighed less than those delivered by cesarean section, except in 11 patients (approximately 20 per cent). If the forces of labor and the period of gestation are similar, it is reasonable to assume that the difference in the infant's weight was the factor that permitted vaginal delivery in many. All infants were term except 2 who were delivered following spontaneous premature labor. The birth weights were 1 pound, 10 ounces and 1 pound, 15 ounces (Fig. 1).

Previous cesarean section cases having prior vaginal deliveries. Of the 84 patients who had at least one vaginal delivery followed by a cesarean section, 58 (69.0 per cent) had one previous section and 74 88 per cent) patients were delivered vaginally (Table VI).

It is interesting to note that of the 26 pa-

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tients who had had two or more previous ci sarean sections and an original vaginal delivery, 84.6 per cent were also delivered vaginally (Table VII).

Of the 130 patients with previous cesarean section, but no previous vaginal delivery, 65.4 per cent delivered vaginally. As the number of sections increases, the percentage delivered vaginally decreases. Fiftysix per cent of the patients with 2 or more sections were delivered vaginally (Table X).

Indications for repeat cesarean section in previous section patients without prior vag-

Table IV. Pelvimetry in patients with cephalopelvic disproportion who were delivered vaginally (49 cases)

Mengert index (%)	Inlet	Midpelvis
65-75	0	0
75-85	5	4
85-95	12	6
95-105	10	13
105-115	11	13
115-125	9	9
125-130	9 2	2
130-135	0	2
Total	49 .	49

Table V. Pelvimetry in patients with cephalopelvic disproportion who had repeat sections (34 cases)

Mengert index (%)	Inlet	Midpelvis
65-75	5	0
75-85	12	9
85-95	10	16
95-105	4	6
105-115	3	3
115-125	0	0
125-135	0	0
Total	34	34

inal delivery. There were 45 patients in this category (Table XI). Cephalopelvic disproportion was the leading cause in 30 (66.7 per cent) of the group. One patient with history of rupture of the uterus at 24 weeks in the previous pregnancy had cesarean hysterectomy at term before the onset of labor . because of an extensive cicatrix of the uterus. One patient with history of repeated stillbirths (Rh-Hr incompatibility), extensive cicatrix of the uterus from 2 previous sections, and history of hypofibrinogenemia had cesarean hysterectomy.

Previous cesarean section patients who had repeat section without labor. Twelve of 214 patients had repeat sections without labor; 3 had placenta previa; 2 had diabetes; 2 had history of prior rupture elsewhere; 2 had absolute fetopelvic disproportion; one had an ovarian cyst; one had a breech presentation and had had 4 previous cesarean sections; one had antepartum death with hypofibrinogenemia developing and had had 2 previous sections. We felt we could not await onset of labor in the first 3 or in the last one, but today we would have awaited onset in the patients with fetopelvic disproportion and those with ovarian cyst and breech presentations, and would have followed these patients in the operating room.

Premature and immature infants delivered from patients with previous cesarean section. Only one infant, or 1.8 per cent, in the group of 56 patients requiring repeat cesarean section was premature (Table XIII). This infant survived, weighing 4 pounds and 8 ounces at 34 weeks' gestation. Cesarean section was necessary because of partial placenta previa. Of 158 patients delivered vaginally, 8, or 5.1 per

Table VI. Vaginal delivery before cesarean section (84 cases—39.24 per cent)

No. of sections Deli		f sections Delivered vaginally Delivere		ered by section To		Total
One previous section	52	(89.6%)	6	(11.4%)	58	(69.0%)
Two previous sections	17	(94.4%)	1	(5.6%)	18	(21.4%)
Three previous sections	3	(60%)	2	(40%)	5	(5.9%)
Four previous sections	2	(67%)	1	(33%)	3	(3.7%)
Total	74	(88%)	10	(12%)	84	(100%)

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Table VII. Original vaginal delivery followed by 2 or more cesarean sections (26 cases)

No. of sections	Delive	ered vaginally		ered by repeat trean section		Total
Two previous sections	17	(94.4%)	1	(5.6%)	18	(69.2%)
Three previous sections	3	(60%)	2	(40%)	5	(19.2%
Four previous sections	2	(67%)	1	(33%)	3	(11.6%
Total	22	(84.6%)	4	(15.4%)	26	(100%)

Table VIII. Indications for repeat section on patients having vaginal delivery before first cesarean section (10 cases)

Indication	Dura- tion of labor (hours)	No. pre- vious sec- tions
Placenta previa	2	2
Cephalopelvic disproportion	5	3
Bicornuate uterus (infant in or horn, placenta in the other) Cephalopelvic disproportion (su total hysterectomy for placen	7 b -	1
increta)	5	1
Cephalopelvic disproportion (pr vious Manchester)	e- 13	1
Cephalopelvic disproportion	7	1
Double footling breech	0	4
Twins-first transverse lie	0	1
Placenta accreta	4	1
Placenta previa (1,000 c.c. rap blood loss)	id 0	3

cent, of the infants were premature or immature, and the mother of each infant had gone into spontaneous labor. Three, or 37.5 per cent, survived. Uncorrected fetal mortality was 2.8 per cent, corrected to zero. Fetal mortality in 214 previous cesarean section cases is shown in Table

XIV.

There were no maternal deaths in the group delivered vaginally. One death occurred 24 days post partum in a patient who had had 3 consecutive cesarean sections for cephalopelvic disproportion. The patient had an infarct in the central point of the low transverse section scar with an exsanguinating hemorrhage at home. She was brought into the hospital moribund. Cardiac massage and intra-aortic transfusions failed to revive this patient.

Table IX. No vaginal delivery before cesarean section (130 cases—60.76 per cent)

	Method of delivery					
No. of sections	- 1	Vaginal	Cesa	rean section		Total
One previous section	57	(71.2%)	23	(28.8%)	_ 80	(61.5%
Two previous sections	24	(64.9%)	13	(35.1%)	37	(28.4%
Three previous sections	4	(36.3%)	7	(63.7%)	11	(8.4%)
Four previous sections	0	,	2		2	(1.7%)
Total	85	(65.4%)	45	(34.6%)	130	(100%)

Table X. Original cesarean section followed by two or more cesarean sections

No. of sections	Deliver	ed vaginally	Delive	red by section		Total
Two previous sections	24	(65%)	13	(35%)	37	(74%)
Three previous sections	4	(36.3%)	7	(63.6%)	11	(22%)
Four previous sections	0		2	(100%)	2	(4%)
Total	28	(56%)	22	(44%)	50	(100%)

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Analysis of complications

Complications encountered for the entire series of 214 cases numbered 24 (Table XV). In 8 patients, secondary inertia developed at the end of the first stage of labor. In 7, one unit of Pitocin in 1,000 c.c. of 5 per cent glucose in water was administered for an average of 35 minutes prior to successful vaginal delivery. In one, because of fetal distress, a repeat section was performed with successful results.

There were 6 cases of abruptio placentae, each of which occurred in the second stage of labor. Two (20 per cent abruption) and one (30 per cent abruption) were delivered without incident of living full-term infants. Two severe cases were managed by breech extraction. Both infants were immature, one weighing 1 pound, 8 ounces and the other 1 pound, $10\frac{1}{2}$ ounces. In the last case of abruptio placentae there was a complete separation accompanied by hypofibrinogenemia. This infant was a term stillborn. The latter 3 account for 50 per cent of the fetal deaths in this series.

Except for one breech presentation which required a cesarean section, all of the patients were managed vaginally. Midforceps extraction was preferred to the Kristeller maneuver because of the uterine scar.

There were 3 postpartum hemorrhages, 2 from retained secundines, and one from secondary uterine atony. In only 7 cases was it necessary to remove an unseparated or trapped placenta.

There were 2 cases of postpartum thrombophlebitis in patients who had had vascular trouble during previous pregnancies; each had had adequate prenatal care.

The average blood loss was 585 c.c. for the patients undergoing cesarean section, and 213 c.c. for those delivered vaginally. These figures include the cases of placenta previa or abruptio placentae. The average blood replacement was 750 for cesarean section and 10 c.c. for the vaginal deliveries.

Incidence of uterine defects in patients of previous cesarean section. Following abdominal or vaginal delivery of a patient who had had a previous cesarean section, the

Table XI. Indication for repeat section in previous cesarean sections without prior vaginal delivery (45 cases)

Indication		No. cases
Cephalopelvic disproportion	30	(66.7%)
Placenta previa	1	
Elective repeat without labor	2	
Juvenile diabetic	2	
Diabetic with transverse lie	1	
Occult rupture	2	
Uterine inertia	1	
Rh-Hr sensitization (stillbirth)	1	(cesarean hysterectomy
History uterine rupture with		
preceding pregnancy	1	(cesarean hysterectomy
Twins-first transverse lie	1	
Double footling breech	1	
Accreta	1	
Pelvic deformity due to trauma	1	
Total	45	

Table XII. Previous cesarean sections who had repeat sections without labor (12 patients)

Indications	No. cases
Placenta previa	3
Diabetes	2
Previous rupture	2
Cephalopelvic disproportion (early in series)	2
Paraovarian cyst	1
Breech (4 previous sections)	1
Antepartum death (erythroblastosis)) 1
Total	12 (5.6%)

Table XIII. Premature and immature infants in series

Weight of infant		t Condition
Deli	vered vaginal	ly (5.1 per cent)
5	lb. 3½ oz.	Living and well
5	4	Living and well
4	13	Living and well
3	6	Died (ABO incompatibility)
1	15	Died
1	10	Died (abruptio placentae)
1	8	Died (abruptio placentae)
1	3	Died
Deli	vered by repe	at cesarean section* (1.8 per cent)
	lb. 8 oz. 34 weeks' ges	Living and well

*Indication, placenta previa (partial).

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Table XIV. Fetal mortality in 214 previous cesarean section cases

	Type	Method of delivery Weight Cause		Cause
1.	Immature, stillborn, intrapartum death	Version and extrac- tion	1 lb. 10½ oz.	Abruptio placentae
2.	Immature, stillborn, antepartum death	Assisted breech	1 lb. 3 oz.	Unknown
3.	Immature, neonatal death	Spontaneous	1 lb. 8 oz.	Abruptio placentae, diabete mellitus
4.	Term, stillborn, antepartum death	Total cesarean hys- terectomy	Unknown	Rh sensitization
5.	Premature, neonatal death	Spontaneous	3 lb. 6 oz.	ABO incompatibility
	Term, stillborn, macerated, ante- partum death	Low forceps	Unknown	Abruptio placentae, chronic discoid lupus

uterus was thoroughly examined manually to ascertain possible defects (Table XVI). No ruptures were found in the vaginal group. There were a total of 30 defects (over 50 per cent were found in classical scars). Ten were unclassified as to type of section, but were probably of the classical type. In an analysis of the type of initial cesarean section scar, 100 (46.8 per cent) were low cervical; 69 (32.3 per cent) were classical; and 9.9 per cent were extraperito-

neal. Type of scar was unknown by history in 24 (11 per cent), but the scars were classical in type.

Uterine rupture in cases of previous cesarean section. There were 2 instances of uterine rupture, both occult (Table XVII). One occurred during labor and the other was unrelated to labor. Labor started in this patient while she was being prepared for cesarean section because of suspected early rupture (an incidence of 0.93 per

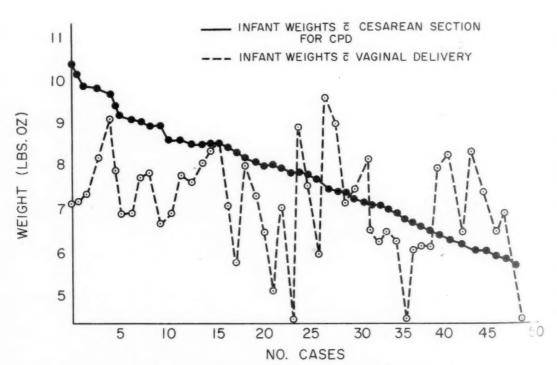


Fig. 1. Comparison of infant weights in same mother delivered by cesarean section because of cephalopelvic disproportion but subsequently delivered vaginally (49 cases).

c(nt). Rupture was suspected in each prior to cesarean section, and repair was accomplished with layer closure at time of operation. Both ruptures occurred in classical scars.

Duration of labor. In patients delivered vaginally, the average length of labor was approximately 8 hours. The longest was desultory labor of 29 hours, the shortest was one hour.

In patients requiring cesarean section, the average labor was 4 hours, the longest a desultory labor of 23 hours, and the shortest, one hour.

Duration of hospitalization. In patients delivered vaginally, the average total days of hospitalization was 10.5 days—7.8 days prior to delivery and 2.7 days after delivery.

In patients delivered by cesarean section, the average total hospitalization time was 19.7 days—an average of 9.9 days prior to delivery, and 10.8 days after delivery.

General comments

Under ideal circumstances vaginal delivery can be accomplished readily in many patients who have had previous cesarean sections. Factors operating to insure safer delivery by cesarean section also operate for safer vaginal deliveries.

Permitting patients who have had previous cesarean sections to go into labor before deciding on type of delivery reduces the incidence of prematurity. With a better developed lower uterine segment, blood loss is less, which assures a better postoperative course for the patient. Amniotomy in early labor may be responsible for the low incidence of spontaneous rupture of the membranes in this series.

Summary

I Two hundred and fourteen consecutive cases of previous cesarean sections were evaluated for possible vaginal delivery. Three fourths of these patients were delivered vaginally.

2 There were 2 suspected occult ruptures which were confirmed at section.

Table XV. Analysis of complications (24 patients)

Complications	No. of cases	Management	
Secondary uterin	ie	Intravenous pitocin	7
inertia	8	Cesarean section	1
Abruptio		Rupture of mem-	
placentae	5	branes	
Abruptio and hypofibrino-		Rupture of mem- branes	
genemia	1		
Breech presenta-			
tion	4	Assisted breech	3
		Cesarean section	1
Transverse arrest	4	Midforceps	
Transverse lie	2	Breech extraction	

Table XVI. Incidence of uterine defect in previous cesarean section (214 cases)

Type of section	No. of defects		
Classical	16		
Low cervical	4		
Unclassified	10		
Total	30 (14%)		

Table XVII. Incidence of uterine rupture in previous cesarean sections (214 cases)

Type	of rupture	No.
Rupture of uter	us, not in labor	1
Complete	0	
Occult	1	
Rupture of uter	rus, in labor	1
Complete	0	
Occult	1	
Total		2 (0.93%)

3. There were no maternal deaths in the group who were delivered vaginally.

4. The fetal mortality can readily be corrected to zero.

5. Vaginal delivery requires less blood transfusion and is devoid of the usual complications potentially attendant on an abdominal operative procedure.

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Discussion

DR. RALPH REIS, Chicago, Illinois. It was of interest to me that in Col. Riva's series, 150 of 200 women with a history of previous cesarean section should be allowed to be delivered spontaneously. I think if one were inclined to be facetious, one could say, "So what?" I hazard the opinion that increased numbers and increased experience will give to Col. Riva the same results that everyone else has, the same incidence of rupture of the uterus, and the same incidence of morbidity and mortality. I can't believe that this is something we should practice or should preach. I cannot understand what is to be gained by permitting vaginal delivery after previous cesarean section. I certainly know what is to be lost.

DR. ROBERT G. DOUGLAS, New York, New York. Col. Riva reached a decision in 1953 to abandon the old dictum "once a cesarean, always a cesarean." In 1957, he published his results in 123 deliveries following cesarean section and indicated that 69 per cent were delivered vaginally with excellent results. The data he has presented today corroborate this experience with 73.8 per cent of his deliveries accomplished through the vagina, including many whose previous section or sections were for cephalopelvic disproportion. It is significant that this was achieved without maternal complication. There were 6 fetal deaths; 4 of these infants were premature, 3 weighing less than 2 pounds. The other 2, term infants, died antepartum. The most ardent proponents of repeat sections could not have surpassed, and may not have achieved these results.

My interest in this subject dates back to the late 1920's as a resident of the late J. Whitbridge Williams at The Johns Hopkins Hospital. At the New York Hospital we have had over 2,000 patients with a history of one or more previous cesarean sections. Through 1959, the actual number was 1,957, of whom 737 were delivered through the normal birth passages. I believe it most significant that not a single infant was lost; nor was there a single instance of a catastrophic maternal complication as a result of a defect or

- 4. Kaltreider, D. Frank, and Krone, William Frank: Clin. Obst. & Gynec. 2: 1029, 195
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rupture of a scar in the lower uterine segment in this large experience. In the earlier years of this period, the classical operation was commonly employed in contrast to the much greater frequency of transverse low cervical operations in the later years. In the year 1959, a total of 234 cesarean sections were performed, and in only 9 of these was the classical technique employed.

Our experience during the decade 1948 through 1957 may be summarized as follows: The number of repeat sections on the private service is approximately 80 per cent as compared to only 50 per cent on the ward service. Of the 981 patients on both services with a previous section or sections, 640 (65 per cent) were delivered by section and 341 (35 per cent) vaginally. In common with Col. Riva's experience, there was one death in this entire group in a patient delivered by repeat section for disproportion, and it too occurred under most unusual circumstances.

During this decade, there were 1,815 cesarean sections, of which 640 (35 per cent) were repeat operations. Marr and Ko have reported 44.7 per cent of cesarean sections at the Woman's Division of St. Luke's Hospital of New York were performed for the indication of previous cesarean section.

A meticulous analysis of every fetal death indicates a slightly higher perinatal mortality on our private service where a larger number of repeat sections were performed. This may be accounted for by a higher incidence of prematurity. Marr and Ko report 11.65 per cent prematurity with the policy of elective repeat sections, while the essayist reports only 5 per cent. Also, there appear to be slightly more problems with pulmonary ventilation in the infant delivered by elective repeat section.

Erhardt and Gold, in a study of cesarean section in New York City for the years 1951 to 1955, found the section rate increased from 3 per cent in 1943 to 5 per cent in 1955. Of the total of 16,949 sections in these 2 years, the indication of previous section was given in 6.710, or 39.6 per cent. There were possibly others

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where another indication was given and no mention made of a previous section. If 40 per cent of sections in this country are done on the basis of previous section, one may extrapolate these figures, assuming the cesarean section rate is 5 per cent for the United States. If there are 4 million births this year, a conservative estimate, there will be approximately 80,000 repeat cesarean sections. In view of these experiences, it would seem reasonable to assume that many of these operations are not essential, and that better maternal and fetal results could be achieved by vaginal delivery.

The philosophy of "once a cesarean, always a cesarean" was promulgated at a time when the classical operation was almost universally employed. Even if this policy were continued for the few patients delivered by the classical technique, it would not alter significantly the large number of patients with this problem.

In many communities in this country, the recent resident is presented with the problem of established local practices. He fears the possibility of medicolegal action and follows community custom which often involves less of the art and science of obstetrics and which is a practice that is unfortunately often more remunerative in some parts of our country. Col. Riva and Capt. Teich have made a contribution which will support the actions of these younger members of our specialty.

Dr. J. P. Greenhill, Chicago, Illinois. The dichotomy between those who believe in "once a cesarean section always a cesarean section" and those who do not, is still sharp, but both groups have a somewhat flexible attitude. If the indication for the first cesarean operation is still present, such as a contracted pelvis, most obstetricians deliver normal-sized babies by cesarean section.

However, in a previous paper on this subject Riva¹ reported that 51.1 per cent of all his patients who had cesarean sections initially for cephalopelvic disproportion were delivered vaginally. Riva stated also that in these cases many infants that were delivered vaginally weighed as much as or more than those delivered by cesarean section. Certainly many of these patients did not actually have cephalopelvic disproportion and could not have had a proper test of labor. Undoubtedly most of these cesarean sections were done before Col. Riva and his associates first saw these women.

Most obstetricians agree that, regardless of the indication, if the previous section was of the classical type it is best to deliver nearly all subsequent babies by elective cesarean section. On the other hand, if a cervical operation was performed, the question will arise as to whether the patient should have an elective cesarean or should be permitted to deliver vaginally.

For several reasons I believe in the dictum "once a cesarean always a cesarean" for most women. The danger of complete uterine rupture after cesarean section is always present and when this occurs there are some maternal deaths and practically all the babies perish. The fact that a patient has had a vaginal delivery after cesarean section is no guarantee that a rupture will not occur subsequently. Furthermore, most ruptured uteri must be removed.

There is no question but that surgical scars in the uterus alter the integrity of the uterus. Regardless of the method employed in closure there is no adequate means of evaluating the integrity of the scar united by connective tissue. There is little justification for subjecting a woman to the hazards of possible rupture and the sequels of severe hemorrhage, especially when the mortality associated with cesarean section is only 0.1 or 0.2 per cent.

On a slide the authors showed that there were 30 uterine defects in the 214 cases (14 per cent). Many of these defects were found after vaginal delivery. What was done about these defects? If no attempt at surgical correction was made, what was and will be the method of conducting future pregnancies and labors in these women?

Formerly, cephalopelvic disproportion and dystocia were the chief indications for cesarean section. Now repeat cesarean section is becoming the most frequent indication for abdominal delivery; hence, in most hospitals there is a gradually increasing incidence of cesarean section. The reverse is true at the Walter Reed Army Hospital because the rate of cesarean section has been reduced to almost half in about 10 years (2.93 per cent versus 1.54 per cent).

Bak and Hayden² found that previous section was the indication for repeat section in approximately 40 per cent of patients at the Chicago Lying-in Hospital where the old adage of "once a section, always a section" is strictly adhered to except for the occasional patient who enters the hospital in well-advanced labor.

It is true that most women with normal pelves who become pregnant after cesarean section can

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be delivered of a live baby with safety through the vagina. However, I am certain that all obstetricians must watch these labors with some trepidation, which is the normal reaction of a conscientious physician.

I want to commend the authors for bringing up this subject again because it bears repeated study and discussion every few years. I am afraid, however, that the difference of opinion concerning the type of delivery after cesarean section will persist because the attitude of most obstetricians is based upon early training and personal experience.

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DR. ROBERT A. Cosgrove, Jersey City, New Jersey. Two of the discussors have mentioned the legal aspects of this particular controversy. This is still a medical controversy and I am very hesitant to have my treatment of patients dictated to me by the legal profession rather than the medical profession. I think we should all do everything we can to maintain the controversy within medical circles and exclude lawyers. There is no justification in my mind for a well-trained obstetrician who sincerely believes that a certain group of patients can be delivered vaginally to be told when he opens his office that in a particular area it cannot be done for fear of lawsuit.

The other comment concerns economic situations. There are people who tell me they cannot handle patients the way they may wish because they cannot get an operating room or cannot put the patient in the hospital long enough. I have not yet found out, however, that they do not take care of central placenta previas or that they have refused to handle ruptured ectopic pregnancies or other serious emergencies.

DR. H. HUDNALL WARE, JR., Richmond, Virginia. The high incidence of successful vaginal deliveries after cesarean sections proves that many first cesarean sections are unnecessary. If all patients with placenta previa, premature separation of placenta, transverse presentations, and prolapse of the umbilical cord were delivered by cesarean section, the increase in the percentage of cesarean sections would probably be less than

one per cent. Absolute cephalopelvic dispropotion is rare. In the patients with borderline diproportion, 6 to 8 hours of trial labor will dcrease the unnecessary cesarean sections.

Dr. Riva (Closing). As for the speaker who would say, "So what?" about such a study. I would say that I am not so much interested in the physician who would say that as I am in the patient who would gratefully acknowledge the effort of the obstetrician in attempting to get her back to normal, particularly when she may have had a previous vaginal delivery. We do not permit our resident staff to go out to less wellequipped or well-organized hospitals to practice this plan of vaginal delivery. It should not be practiced unless an ideal situation exists, and in most of our hospitals the ideal situation does not exist. Dr. Frank Kaltreider of this Association recently, quoted Russell, in an article, thusly, "If you have an opinion about any matter, it should be based on ascertained facts, not upon hope, or fear, or prejudice!"

The question has been raised elsewhere whether the art of obstetrics is being lost to the craft by surgery. This is something we overlook.

Today most of the comments were made about the immediate problem but there are other points to consider. What about transfusion reactions? It goes without saying that the patients undergoing repeat section do get more transfusions and, therefore, there are remote transfusion reactions. Our hematologist tells us today that the morbidity and death rates from hematologic reactions are as great as from acute appendicitis. Dehiscence does occur and it is debilitating. I do not think any of us would argue that the second, third, fourth, and fifth incisions into the uterine segments become a very disconcerting matter. We should be alert to the possibility of intestinal complications, and they do occur although many of them are at a remote date. Today one of the most fearsome situations we face is the problem of intestinal obstruction in future pregnancies.

In answer to Dr. Greenhill's question about uterine defects, I can state that we are studying this problem with both hysterography and the use of an intrauterine balloon technique in the 6 to 10 weeks' postpartum period. This technique is similar to that used in studies being conducted in Australia and Germany, as mentioned explient by Dr. Leon Israel.

Results in the management of preclinical carcinoma of the cervix

J. P. A. LATOUR, M.D.

Montreal, Quebec

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DURING the 10 year period 1950 to 1959, 274 cases of preclinical carcinoma of the uterine cervix were diagnosed at our institution as a result of cytologic screening and the application of ring biopsy⁵ to the cases with positive cytology findings. There were 136 cases of carcinoma in situ (International Stage 0) and 138 cases of early invasive preclinical carcinoma similar to those referred to by Wheeler and Hertig9 as "clinically unsuspected carcinoma of the cervix." The early invasive preclinical group belongs to International Stage I by definition, but inclusion of these early invasive preclinical lesions with clinically evident Stage I tumors creates, we believe,6 problems in reporting, for it is obvious that a clinic which has the benefit of widespread cytologic screening will have a Stage I composition very different from that of the clinic which receives patients essentially on the basis of symptomatology.

Kottmeier,² reporting on the results obtained in the treatment of 98,218 cases of carcinoma of the cervix calls attention to the difference in results from the management of early Stage I as opposed to later Stage I cases, and in a later publication³ he suggests a modification of the International classification as shown in Table I. We would welcome such a modification because our 138

cases of early invasive preclinical carcinoma would fit neatly in Stage Ia of the proposed classification.

Material

There were 273 cases of squamous carcinoma in our group of 274 preclinical cancers of the cervix. The solitary case of preclinical adenocarcinoma detected by cytology indicates that this screening technique is inadequate in detecting early adenocarcinoma because there would have been over a dozen cases if we base ourselves on the 4.97 per cent incidence of adenocarcinoma in our complete series of cervix tumors.⁸

The age of the patients varied widely, as shown in Table II. This table includes, for purposes of comparison, the ages of 146 clinical Stage I lesions seen during the same 10 year period as the preclinical lesions. Perusal of Table II reveals a wide variation in age incidence which does not differ significantly in the three groups. It is a matter of coincidence that the youngest patient in each of the three groups was 20 years old. The average age of patients with early invasive carcinoma was only 1.6 years older than those with carcinoma in situ-an increment which may not be significant because of the widely varying ages of the patients. The average age of clinical Stage I patients was some 10 years older than those with preclinical lesions, and, at 47.7 years, is higher than expected for this group. The usual average age of Stage I patients, 43.3 years, is obtained when we combine those with clinical and those with preclinical le-

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Presented at the Seventy-first Annual Meeting of the American Association of Obstetrics and Gynecology, Hot Springs, Virginia, Sept. 8-10, 1960.

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Table I. Present and proposed stages of carcinoma of the cervix

A.	Present classification	Pro- posed classifi- cation
Stage 0	{ classical type } with suspected invasion	0
Stage I	preclinical carcinoma	} Ia
Stages II to IV	clinical carcinoma	Ib II—IV

Table II. Age distribution

	No. of pa-tients	Young- est	Old- est	Aver-
Carcinoma in situ				
(Stage 0)	136	20	74	37.1
Early invasive pre-				
clinical cancer	138	20	71	38.7
Clinical cancer local-				
ized to cervix	146	20	76	47.7
Stage I International				
(line 2 plus line 3)	284	20	76	43.3

Table III. Summary of methods of management

	Carcinoma in situ (Stage 0)		Early inva- sive preclini- cal cancer		
Type of treatment	1950- 1954	1955- 1959	1950- 1954	1955- 1959	Total
Radiation only Radiation and	2	2	40	7	51
operation	3	1	19	6	29
Total operation	7	16	10	12	45
Operation with conservation of ovarian function	23	47	15	24	109
Ring biopsy only; no definitive	43	17	13	44	103
treatment	16	18	4	2	40

sions, which makes it probable that the usual Stage I group contains a significant number of early invasive preclinical lesions.

Management

Our 274 cases of preclinical carcinoma were managed on an individual basis after close cooperation between the clinician and the pathologist. The necessity for this joint management has been recently emphasized. There were actually 15 different methods of treatment but inasmuch as several of these were along the same lines we have reduced the number of management groups to five by combining essentially similar approaches. Table III summarizes our management in a tabular fashion, the entire group has been divided into two 5 year halves in order to indicate trends in management.

Perusal of Table III reveals that radiation was used more frequently in the treatment of the early invasive lesion than the in situ cancers, as one would expect. It also shows that radiation was used much less frequently in the second 5 year period than it was in the first. "Total operation" here means total hysterectomy and bilateral salpingo-oophorectomy and Wertheim operation; in both cases all ovarian tissue was removed. Although Table III shows no significant trends in this group we may state that the Wertheim operation was performed for early invasive cancer on 3 patients during the first 5 years and no patient was treated in this manner in the second 5 years. Operation with conservation of at least one ovary was practiced 38 times in the first 5 years and 71 times in the second. The significant trend in our management has been toward less radiation and more operation with ovarian salvage. The number of patients managed with ring biopsy alone has not varied in the two groups, but it is obvious that we are inclined to manage a carcinoma in situ with no definitive treatment more often than we are inclined to take a chance on an early invasive lesion.

Results

We have follow-up information to date on 273 of the 274 patients in this series. The results of individual management are summarized in Table IV. Some of the items in Table IV merit further discussion. Two of the patients with recurrent positive cyto ogy after definitive treatment had been treated with radium only, and the subsequent hy terectomy specimen failed to show residual tumor. The third patient had a recurrence

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of carcinoma in situ adjacent to the vault scar after hysterectomy; she was treated with a radium plaque and remains apparently well to date. (This patient also appears in Table IV as the case of proved recurrence.) The fourth patient in this group had a total hysterectomy and currently shows suspicious cytology, there is no clinically evident recurrence, and the Schiller test shows no suspicious areas in the vault of the vagina. This patient is not included in the 263 listed as alive and apparently free of tumor. These 4 cases with recurrent positive cytology all belonged to the early invasive group. There were no cases of recurrent positive cytology after definitive treatment in the Stage 0 group. Carter and associates1 have made a similar observation in their series.

Of the 2 patients with recurrent positive cytology after ring biopsy only, one became cytologically negative after a few months and remains so, the other had a hysterectomy but no tumor could be found in the specimen.

The patient with presumed tumor recurrence was treated in 1952 with radium and x-ray. Within one year she had induration on one side of the pelvis and was presumed to have recurrent tumor. A second course of deep x-ray therapy was given and the patient survives today still with some induration to the pelvic wall 8 years after treatment.

The serious complications include 2 patients with ureterovaginal fistulas following Wertheim operations. Both patients had nephrectomies on the side affected and are now well. Two patients had severe radiation proctitis, one after 3,000 mg. hr. of radium, the other after 3,500 mg. hr. Since neither of these patients responded to conservative management, both were subjected to posterior exenterations and are now well. These 4 serious complications all occurred in the first 5 years of the study and no doubt influenced our drift away from the use of radium and Wertheim operations in these early cases of cervix cancer.

There were a total of 13 pregnancies associated with the series. Five patients were

pregnant at the time of diagnosis. Two of these early pregnancies were sacrificed in definitive treatment by total hysterectomy, the other 3 were allowed to go to term. Eight women became pregnant after diagnosis and conservative management, 5 went to term, 2 aborted, and one had an ectopic pregnancy. A total of 8 babies survive as a result of conservatism.

Eight patients are known to have died; all were under follow up and had no evidence of recurrence of the tumors of the cervix when last seen. Three of these patients died of other primary malignant lesions, all proved, as follows: one case of primary adenocarcinoma of the ovary, one case of breast cancer with axillary metastases, and one case of astrocytoma after craniotomy. In the remaining 5 cases, there were no autopsies and the causes of death were presumed to have been as follows: 3 "heart failure," one acute damage of the brain stem, and one unknown.

The results shown in Table V are based on the severest criteria. Patients lost to

Table IV. Summary of results of management

Total number of patients	274
Patients lost to follow up	1
Recurrent positive cytology after de-	
finitive treatment	4
Recurrent positive cytology after ring	
biopsy only	2
Proved tumor recurrence	1
Presumed tumor recurrence	1
Serious complications of treatment	4
Number of pregnancies in series	13
Died of other causes, pelvis free on	
follow up	8
Presumed to have died of cancer of	
cervix	0
Alive and apparently free of tumor	263

Table V. Results-1950 to 1954, inclusive

	No. of pa-tients	Survi- vors 5 years	Survi- vors %
Stage 0	51	49	96.1
Early invasive preclinical	88	84	95.4
Clinical Stage I	52	38	73.1
International Stage I	140	122	87.1

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follow up are presumed dead of tumor and patients dying of proved intercurrent disease before 5 years are also counted as dead of tumor. Patients who have died of presumed other causes without proof are counted as dead from tumor. Only those patients known to have lived 5 years without evidence of tumor are counted as 5 year survivors. The figures in Table V also include our results in clinical Stage I cases from 1950 to 1954 for comparison.

It is evident from perusal of Table V that preclinical cancer yields a good survival rate. For practical purposes, in the management of our current cases we consider our survival rate to have been virtually 100 per cent inasmuch as no patient in the entire group appears to have died from cancer of the cervix to date. It is interesting to note that when the early invasive preclinical tumors are omitted from Stage I the survival rate is only 73.1 per cent, but when these are included, our result for what would correspond to International Stage I is 87.1 per cent 5 year survivors. It appears that we should henceforth question the composition of Stage I in statistical reports.

Conclusions

As a result of the analysis of this group of 274 patients with preclinical cancer of the cervix, we are prompted to make the following conclusions:

1. Routine cytologic screening has detected a relatively large number of preclinical squamous cancers of the cervix but appears to have missed the early adenocarcinomas.

- 2. Both preinvasive and invasive preclinical carcinomas are recognized. These should be separated and identified for the sake of uniform statistical reporting. In this respect there appears to be a need for modification of the International Classification, as suggested by Kottmeier.
- 3. Both the average age of the patients and the response to treatment indicate that early invasive preclinical cancer is closer kin to carcinoma in situ than to clinical carcinoma. The clinical appearance of the cervix would seem to be an important factor in prognosis.
- 4. Preclinical cancer of both varieties responds well to a variety of treatments. Management should be individualized after close cooperation between the experienced clinician and the pathologist. There appears to be very infrequent need for radiation therapy or radical surgical procedures.
- 5. The definitive treatment of choice appears to be total hysterectomy with a wide vaginal cuff and conservation of ovarian function when practicable.
- 6. The degree of therapy inherent in complete circumferential biopsy procedures appears to offer the young woman desirous of further pregnancies adequate security, and we recommend this course provided the patient and her husband understand the risks involved and accept perpetual periodic cytologic screening as the only method of protection.

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Discussion

Dr. BAYARD CARTER, Durham, North Carolina. Dr. Latour's series of 274 patients with

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preclinical carcinoma of the uterine cervix includes 136 Stage 0 carcinomas and 138 patients with early invasive preclinical carcinomas.

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He correctly stresses that even though these 13b cases of early invasive preclinical carcinomas belong in Stage I, their inclusion in the statistics for Stage I cancer would lead to confusion in the reporting of the results in the treatment of Stage I cancer. He proposes that these 138 cases might be listed in the Stage I classification as Stage Ia as suggested by Kottmeier.

He also notes that in his total of 274 patients with preclinical carcinoma of the cervix 273 had squamous carcinomas and only one had preclinical adenocarcinoma. He suggests that this fact indicates that the screening technique is inadequate in detecting early adenocarcinomas of the cervix. With this we agree. However, we note that even though the cytologist may not be able in many patients to state that adenocarcinomas are present, yet the smears warrant a classification grouping which makes mandatory proper biopsy techniques for tissue for histologic study.

The perusal of his therapy justifies his statement that preclinical cancer of both varieties responds well to a variety of treatments. He also emphasizes that the management must be individualized with close cooperation between the clinician and the pathologist.

For what they may be worth, the results in our clinic follow in brief summary form. From Jan. 1, 1947, to Dec. 31, 1959, the diagnosis of Stage 0 (intraepithelial cancer) was made in 550 patients. In these 550 patients 65 patients were excluded from the intraepithelial group because:

- 1. Fifteen were proved in less than one week to have invasive cancer by histologic study of multiple block sections.
- 2. Nineteen were proved to have invasive cancer in from 1 to 6 weeks.
- 3. Eleven were proved to have invasive cancer in from 2 weeks to 10 years.
- 4. Fourteen had microscopic foci of invasion and were treated as invasive cancer. They were, however, for statistical purposes of reporting, put in a separate group and are not included in our statistics for salvage for Stage 0 or of Stage I cancer.
- 5. Six patients were treated for invasive cancer and are not included in the statistics for Stage 0 or Stage I cancer.

In 70,584 gynecologic patients, intraepithelial cancers were diagnosed in 421 and invasive cancers in 1,245. This gave the occurrence rates for intraepithelial cancers 0.60 per cent and for in-

vasive cancers 1.77 per cent. In 10,053 obstetric patients there were diagnosed 64 intraepithelial cancers. This gave an occurrence rate of 0.64 per cent. Thirty-one invasive cancers were diagnosed, an occurrence rate of 0.31 per cent.

In attempting to evaluate microscopic foci of invasion in the biopsy slides certain criteria were adopted and were strictly observed. By "focus of invasion" our pathologists mean a microscopic area of intraepithelial cancer which extends into the underlying tissues and which is free of the confining influence of the so-called basement membrane. An extension of the tumor into the submucosa which remains confined by the basement membrane in a compact mass is called an invasive bud, but it is not considered as a focus of invasion or as invasive cancer. The growth of the intraepithelial cancer into the endocervical glands or the extension of the intraepithelial cancer along endocervical epithelium to the endometrial epithelium is not considered as indicating invasive cancer.

Thus far in our series we have 22 patients with the diagnoses of microscopic foci of invasion. Fourteen were treated for Stage I cancer and are not included in our statistics for Stage 0 or Stage I cancer and are held in a separate group for further observation and study.

Eight patients, 7 gynecologic and 1 obstetric, had microscopic foci of invasion in the cervix at hysterectomy or at trachelectomy. These 8 patients are not included in our statistics for Stage 0 or Stage I cancer and are also held in the separate group. To date none of these 8 patients has shown persistence of atypical smears or signs of persistent or recurrent cancer.

Certainly, with the increased interest in these patients with microscopic foci of invasion and with more extended pathology study of the tissues by multiple block techniques, the incidence of these microscopic foci of invasion will steadily increase.

It is a high tribute to Dr. Latour's interest and to his attainments in gynecologic pathology that in 274 patients he was able by diligent pathology efforts to find 138 early invasive preclinical carcinomas. We will follow with sincere interest the reports on the subsequent course of these patients. It was a pleasure to read this paper and to attempt to discuss it.

Dr. Frank R. Smith, New York, New York. Dr. Latour has presented a report on the study of 274 patients with preclinical cancer of the

cervix, diagnosed as the result of cytologic screening and application of ring biopsy during the 10 year period 1950 to 1959. For comparison he has divided the patients into the 5 year periods (1950 to 1954 and 1955 to 1959) when the patients were first encountered. He does not state the total number of patients actually screened and, if they were asymptomatic, whether they were seeking hospital or medical help for any reason.

It has been repeatedly shown that experienced pathologists do not always agree on the pathologic interpretation of slides classified as Stage 0 in situ and as so-called preclinical invasive cancer. From the findings of this and other studies, it would seem that the so-called preclinical early invasive group would be more accurately classified statistically with the Stage 0 in situ lesion group rather than with the real invasive cancer group (International Stage I). I would suggest that the preclinical early invasive group be eliminated from the International Stage I group and be kept with the precancerous lesions where they rightfully belong. Call them Stage 0 and Stage 0a if you wish. Otherwise our statistics will continue to be confused and our quest for knowledge about true cancer of the cervix will be retarded.

The unfortunate complications of drastic therapy for these precancerous lesions are to be deplored (11.7 per cent fistulas).

The excellent results of 8 living babies salvaged from 13 pregnancies as the result of conservative therapy is praiseworthy.

DR. MICHAEL J. JORDAN, New York, New York. In discussion of Dr. Latour's paper, a number of points may be raised. Although it is agreed that Stage I should be divided into preclinical invasive carcinoma (microcarcinoma) and clinical carcinoma, it would be unwise to have advanced cases of in situ carcinoma included in Stage I rather than in Stage 0. In those cases of carcinoma in situ with suspicion of invasion, wide conization of the cervix should be done, the entire cone blocked and studied by step and/or serial section. This would establish a definitive diagnosis and permit more accurate staging before further treatment is instituted.

The age variation shown in Dr. Latour's Fig. 2 agrees with most series. The average age of patients with carcinoma in situ is 37.1 years, approximately 3 years younger than the average age of patients with carcinoma in situ in our

study group. This again poses the problem of definite criteria for the diagnosis of this less in since in many borderline cases pathologists will still disagree on what actually constitutes the lesion called carcinoma in situ.

There are degrees or gradations of carcino nain situ in the Stage 0 group. In our study series we feel that we have a preponderance of early cases of in situ carcinoma. The population from which our study cases derive is predominantly asymptomatic, which probably accounts for this. Comparison of the behavior of early in situ lesions and full-blown in situ lesions with marked gland duct extension may possibly lead to erroneous conclusions. This simply points up the necessity for continuance of prospective studies of this lesion so that accurate information regarding its behavior may be drawn.

The small age difference of 1.6 years between the patients with in situ carcinomas and those with preclinical invasive carcinomas reported by Dr. Latour may be a reflection of the fact that the in situ lesions in his group may be fully developed lesions which had existed for a number of years prior to their detection. Another factor may be failure on the part of pathologists to recognize what constitutes true invasion. Marked gland duct extension is sometimes mistaken for true invasion.

We do not advocate the use of irradiation as a method of treatment for the in situ lesions. In the younger patients we have advised wide conization of the cervix with step and/or serial section of the cone followed by close follow-up with smears; in the older patients total hysterectomy has been done except on those few who desire further pregnancies. Bilateral salpingo-ophorectomy is not performed routinely. Thus, we agree with Dr. Latour's present trend toward more conservative operations as is shown in Table III.

We strongly believe, however, that preclinical invasive carcinoma (microcarcinoma) should be treated as invasive carcinoma. The difference between microcarcinoma and gross extension is simply a matter of time interval. The time interval will depend to a large extent on the grade of the tumor. Microcarcinoma indicates that the tumor has all the potentialities of metastasizing by either lymphatics or blood vessels. Our feeling is that the so-called in situ carcinomas that have been reported as metastasizing would have proved to be microcarcinomas had proper step and/or serial sections been done. Therefore the

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treament of microcarcinoma should be radical operation, irradiation, or a combination of the two modalities. Unless the patient adamantly refuses trea ment we would not follow any case of established preclinical invasive carcinoma by observation alone. The cytologic interpretation of smears following irradiation therapy is extremely difficult and this may explain the failure to find residual tumor in the surgical specimen in the 2 cases showing positive cytology after treatment with radium. The recurrence of carcinoma in situ in the vaginal vault following hysterectomy described in the third patient is a more serious problem. It is difficult to determine whether this constitutes recurrence or whether a new in situ lesion develops.

Serious complications following radical operation for carcinoma in situ was one of several reasons which prompted the initiation of our prospective study of in situ carcinoma in 1950. The results of our 10 year study indicate that radical operation is unnecessary where there is a well-established diagnosis of carcinoma in situ. It appears that Dr. Latour's group is now in agreement with this.

In our study group we have a 1 per cent incidence of adenocarcinoma of the cervix. We do not believe that this small incidence can be attributed to inadequate screening techniques, but we feel Dr. Latour's projected incidence is too high.

Dr. R. W. Mohler, Philadelphia, Pennsylvania. When this discussion was prepared I had not had the opportunity to review Dr. Latour's paper and my discussion is based entirely on the summary of his presentation in the official program.

In the considerations given preclinical carcinoma of the cervix there has been almost no thought given to the histologic and clinical changes which evolve slowly from pre-existing and minor anomalies or disease of the cervix. I have particularly in mind the so-called congenital and traumatic eversions of the cervix which I have referred to in the literature as areas of misplaced endocervical tissue. The misplaced endocervical tissue, if allowed to remain, produces inflammatory changes at the squamocolumnar junction which are easily recognized clinically and histologically. The changes which occur at this abnormal site of juncture are evident in various epithelial changes which can be interpreted differently by almost every observer.

We have no way of knowing that all abnormal or diseased cervices are not preclinically malignant. We can therefore not select from abnormal or diseased cervices cases to treat because they may be preclinically malignant. Our attitudes should be to establish a standard for a normal cervix and study, restore, or treat all cervices which do not conform to that standard of normal.

It is my impression that most cervical disease that is recognized clinically originates from congenital or traumatic misplacement of the endocervical mucosa and that because of this misplacement a persistent inflammatory reaction evolves. This reaction could be associated with the abnormal habitat of the misplaced columnar epithelium. Because of this attitude, I have felt that it is necessary to destroy the misplaced endocervical tissue and revise the juncture point of the squamocolumnar tissue so that the columnar tissue will be protected from the abnormal habitat of the vaginal secretion.

In our clinic at the Methodist Hospital, of which Dr. Hahn is now the chief and which I formerly directed, we have utilized this attitude in the management of all congenital or traumatic eversions or erosions or what I choose to call areas of misplaced endocervical tissue for many years.

In this particular clinic our incidence of carcinoma of the cervix is very low. Its ratio to carcinoma of the endometrium is about 1 to 10. The explanation for this experience could be discussed indefinitely, but in my opinion it is because we treat the cervix on an average of 20 years before carcinoma becomes clinically apparent. It is very significant that almost all individuals in the department share my attitude and recognize and manage cervical disease in the same way.

Certain standards for the normal cervix have been established and when the appearance and clinical impression of the cervix does not meet standards which we have established as normal they are considered as diseased. The cervix is treated by destruction of the misplaced endocervical tissue in such a way that the squamocolumnar juncture of tissue will be protected from the habitat of the vaginal canal. At the time of treatment adequate tissue is secured for histologic study.

Dr. Frank R. Lock, Winston-Salem, North Carolina. We are quite aware of the differences

in criteria used by various pathologists in the diagnosis of intraepithelial carcinoma of the cervix, intraepithelial carcinoma wth minimum invasion, and early invasive carcinoma. It is unfortunate that these diagnoses are variable from one center to another, and, if made by a general pathologist, often are in error. Our interpretation of tissue usually differs from that of the general pathologist.

Another problem relative to carcinoma of the cervix is our inability to evaluate the biologic characteristics of the tumor or evidence of host resistance on the basis of tissue examination. In the past 18 months we have been doing peripheral blood studies on patients with carcinoma of the cervix and have been surprised to find tumor cells in the circulating blood in more than 20 per cent. We are quite aware that the significance of this is unknown and that the fate of the tumor cell in the peripheral blood is far from definite. However, it is a significant finding and represents something of the biologic characteristics of this tumor which usually is considered a tumor that is localized and one which spreads principally by lymphatic extension.

In a recent patient a positive smear led to conization of the cervix. The tissue showed a microcarcinoma, but with definite invasion. At the time of a primary radical procedure performed 48 hours following the conization, blood was taken from the local venous drainage which showed tumor cells. Intensive study of the specimen revealed no residual tumor.

In May, I reported our experience with 184 patients with Stage I invasive carcinoma of the cervix. We use substages, and Stage Ia is preclinical or microcarcinoma which includes Stage 0 with minimal or superficial invasion. Of the 184 patients, 29 were treated by primary radical hysterectomy with regional lymphadenectomy. Of 5 patients with Stage Ia lesions (preclinical or microcarcinoma), lymph node metastasis was found in one patient. In Stage Ib (clinical lesions of 1 cm. or less), 3 of 17 patients had lymph node metastases. In 7 patients in Stage Ic, a well-developed Stage I carcinoma of the cervix, 3 had lymph node metastases demonstrated on pathologic examination. Either this indicates different biologic characteristics in this group of patients as compared to those reported by Dr. Latour, or perhaps, as the years go by, Dr. Latour may find a number of patients who had lymph node metastases at the time of the original operations, as indicated in the lymph nodes.

Dr. J. Edward Hall, Brooklyn, New York, I would like to present to you our experience with carcinoma in situ which I hope will tend to complement Dr. Latour's presentation. In 1950, our clinic embarked upon a prospective study to see what would happen with carcinoma in situ and established the policy not to treat patient in whom the diagnosis of carcinoma in situ had been established. This diagnosis was established after a complete tissue examination of the cervix and the endometrium. These patients were then examined every 3 months in the follow-up clinic by history, physical examination and cytology measures, and once a year by re-examination of the cervical tissue. Through June, 1959, we had 134 such patients who fell into this group of carcinoma in situ. Because of other gynecologic organic problems which in themselves necessitated therapy or because the patient did not elect to be followed, we wound up with 89 patients who did not receive any initial therapy. Of these patients we now have 56 who are still untreated. The remaining patients have been treated because they developed conditions such as ovarian cysts or other organic conditions which necessitated therapy, or again they refused to be followed.

I think it is of interest that in this group of 134 cases of carcinoma in situ, 60 per cent of the patients had no symptoms and 57 per cent of the patients had no organic evidence of any gynecologic problem. Twenty-five per cent had the diagnosis initially because of cytologic screening and 27 per cent because of a random biopsy at the time of an incomplete abortion, which is one of our routine procedures. Thus, in over 50 per cent of our patients carcinoma in situ was initially diagnosed because of a routine examination of the cervix with no evidence of symptomatology referable to it. This, I think, complements not only Dr. Latour's remarks but Dr. Jordan's and Dr. Carter's.

Of these 134 patients, only one, so far as I know—and we have followed every one of them—has developed any evidence of invasion. This was a so-called microinvasion and after we reviewed the slides we thought it might have been debatable as to whether it should have been classified in this category originally.

I would throw a word of caution into any conclusion from this effort that carcinoma in situ apparently is not the serious disease which some people would indicate. We must be aware that in the diagnostic procedures we employ, we may

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inadvertently treat the patient and consequently we believe that many of these patients with carcinoma in situ who at the moment show no evidence of recurrence or invasion probably have been cured by our extensive diagnostic procedures. This is an important thing to bear in mind when one hears about carcinoma in situ being a disease that can be followed.

DR. ARTHUR T. HERTIG, Boston, Massachusetts. I have listened to the discussion with great interest and I have only two points to emphasize. One, which was already highlighted by Dr. Carter and Dr. Lock, is the disagreement on the criteria of carcinoma in situ. I think before invasion occurs it is a little difficult actually to make the diagnosis, but we do make the diagnosis on the basis of the fact that the lesions have an appearance similar to those which ultimately invade. Hence, the criteria were gained by a retrospective study. I would agree, although I am a pathologist, that pathologists in general tend to overdiagnose this lesion. I think we do not yet have all the proper morphologic criteria which will enable the competent pathologist to make an accurate diagnosis of carcinoma in

Nevertheless, if one looks at the whole spectrum of cervical changes from the initial lesion in the young married or unmarried woman in these ectopic or displaced areas of the endocervix spoken about by Dr. Mohler clear up to Stage IV carcinoma, there is a series of gradual changes merging one into another. I was glad to hear Dr. Latour point out that there are gradations from carcinoma in situ to questionable invasion to microinvasion and into overt carcinoma.

The only thing that I think I can perhaps add is to say what I personally think about how these several parts of the spectrum should be put in the classification. I think there is such a thing as carcinoma in situ whether we can precisely diagnose it or not. I think it is treatable by simple hysterectomy with conservation of the ovaries once one has done either conization or multiple biopsies to rule out even a suggestion of invasion or microinvasion. Of course, I could not agree more heartily with Dr. Jordan, who said that the minute there is microinvasion it is possible for the first bud to get into the lymphatics. It does not ordinarily but it can and, therefore I believe wholeheartedly that once there is definite microcarcinoma, no matter how small it is, it is a different disease than carcinoma in situ, even though it is related to carcinoma in situ and is derived from it.

I was delighted to have Dr. Lock describe 1 out of 5 lymph nodes involved in microcarcinoma. I would like to emphasize that one can tell about true microcarcinoma only by a combination of multiple biopsies or in conization and serial blocking with, on occasion, true serial sections of a given suspicious area. In a series of carcinoma in situ, about 8 per cent of a combination of serial blocking and serial sections of the suspicious block will prove to be actual microcarcinoma.

In summary I would reiterate that, although microcarcinoma is a very tiny affair and that in general it has a 20 per cent better prognosis than Stage I grossly visible types, I still think it is carcinoma and to separate it out from the whole spectrum and put it separately or call it carcinoma in situ is like saying that the first 10 seconds of a long race, although different than the rest of the race, are not part of that race. So I would like to emphasize again that microcarcinoma is carcinoma, even though it has a good prognosis.

Dr. Clyde L. Randall, Buffalo, New York. It has been evident for years that the results of the treatment of carcinoma of the cervix parallel the percentage of early cases in any series reported. This has certainly been true in the results reported from the Roswell Park Institute in Buffalo. While I am impressed by Dr. Hertig's conviction that these early changes might well be regarded as the beginnings of a fatal disease, it is also evident that we should remember Frank Smith's emphasis and make certain that we designate the noninvading in situ stage of carcinoma as something other than carcinoma of the cervix. Perhaps we should be increasingly critical of the results now being reported in the treatment of cervical carcinoma.

The effect of including equivocal lesions may be suspected in the reports of the Division of Cancer Control of the Department, of Health of the State of New York. It seems too good to be true that in their published data there appears to have been, from 1933 to 1953, so much as a 40 per cent reduction in the number of deaths due to carcinoma of the cervix among the Upstate New York population of approximately 21/2 million adult women. A year ago Dr. John Graham instituted a review of the "cured cases" of cervical carcinoma that had been reported by western New York hospitals other than the state institution. His study, reviewing the years 1950 to 1954, has been completed and will soon be published. Graham and Nichol's data suggests that as many as 20 to 25 per cent of the lesions originally reported as carcinoma of the cervix were in reality equivocal lesions that present day criteria would regard as in situ carcinoma.

DR. LATOUR (Closing). It is obvious that the crux of the problem under discussion is the delineation of what constitutes a diagnosis of carcinoma in situ and what constitutes the diagnosis of invasion.

Dr. Smith asked how many patients vere screened for our 274 cases. We have had over 100,000 patients screened for this study.

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Critical points of failure in the therapy of cancer of the cervix

A study of 250 recurrences

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EQUINN W. MUNNELL, M.D.
WALTER A. BONNEY, JR., M.D.
New York, New York

This is a study of recurrent carcinoma of the cervix, of when it recurs, perhaps why it recurs, where it recurs, the treatment of the recurrences, and the salvage rate obtained from treatment of these recurrences at the Columbia Presbyterian Medical Center (Sloane Hospital for Women) and the Francis Delafield Hospital in New York City during the years 1940 to 1957.

The extremely unhappy end results in the treatment of this series of 250 cases of recurrent carcinoma of the cervix will serve to emphasize two factors long recognized as essential in the management of gynecologic cancer. These are that improved cure rates depend upon early diagnosis and that the primary treatment is the only one offering a significant chance of cure.

Material

The study is confined to those cases of recurrence seen in the years 1940 through 1957 at Presbyterian and in the years 1951 through 1955 at the Francis Delafield Hospital. It includes 151 cases that originally

were epidermoid Stages I or II at these hospitals, 27 cases originally adenocarcinomas of the cervix at these hospitals, and a group of 72 cases that were either originally epidermoid Stage III at these institutions and thought to have undergone real remission before recurrence or that had been treated elsewhere and were seen at these institutions for treatment of the recurrence. They are summarized in Table I. The study, in contradistinction to most, is not of patients with recurrences thought favorable for treat-

Table I. Original stages of all cases in this study

Stage I	70
Stage II	81
Adenocarcinoma	
Stage I	17
Stages II, III	10
Stage III (thought to have	
had remission)	32
Recurrent cases whose primary	
treatment was given elsewhere	40
Total	250

From the Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons and the Presbyterian Hospital (Sloane Hospital for Women), and the Department of Gynecology of the Francis Delafield Hospital.

Presented at the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960. ment but of all recurrences. The heterogeneous aspect of the material can be defended on the grounds that it does anything but lend to the aura of success in the management of recurrent carcinoma of the cervix in our institution, for, of these 250 patients, only 5 survived 5 years after treatment of the recurrence.

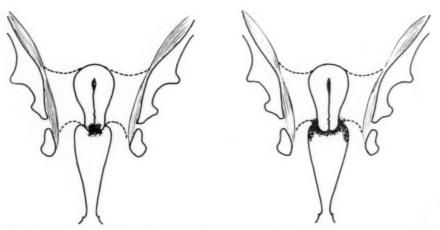


Fig. 1. Type A, central pelvic type of recurrence of carcinoma of the cervix (17 per cent).

Table II summarizes the success of others in the salvage of recurrent cervical cancer. None of these series consists of their total recurrent cases but of the recurrences treated and are therefore selected cases except for the series of Calkins,2 Murphy and Schmitz,9 and Van Herik.14 Another difficulty is the fact that the definition of recurrence varies from author to author. Our own criterion for recurrence was one negative pelvic examination following completion of treatment. Obviously, this has probably resulted in the inclusion in this series of a number of cases of persistent or residual disease. However, it must be argued that most recurrences are really cases of residual disease.

Sites of recurrence

Classification of sites of recurrence and their relative frequency. We have classified sites of recurrences in a manner somewhat similar to the classification of Brunschwig and Daniels³ but the use of a letter to designate the exact site has made it more specific. It has proved to be a very workable and precise classification.

1. Central pelvic recurrences are those clinically thought to be limited to the cervix and/or vaginal vault and designated in this study as Type A (Fig. 1). These are the most favorable for re-treatment but made up only 17 per cent of the total number of recurrences.

Table II. Salvage rates of others in treating recurrent cervical cancer

Year	Author	No. of cases	Selection	% survival	Type of treatment
1948	Calkins	72	Unselected	9.7	Radiation
1949	Truelson	216	Selected	3.7	Radiation
1953	Kottmeier	29	Selected	34.5	Operation
		87	Selected	36.8	Fulguration (cervix only)
1955	Parsons and Taylor	45	Selected	22*	Exenteration
1955	Van Herik	110	?	16.4	Radiation
1956	Brunschwig and Daniels	111†	Selected	15	Exenteration
1956	Murphy and A. Schmitz	44	. ?	16	Radiation
1957	Graham and Hendrix	100	Selected	5	Operation and radia tion
1957	Schmitz et al.	50†	Selected	23.5*	Exenteration
1959	Love	96	?	4*	Radiation
		22	Selected	40*	Operation

^{*}Less than 5 year follow-up.

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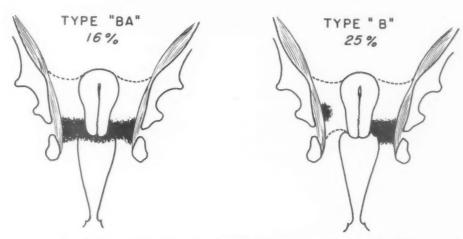


Fig. 2. Deep pelvic type of recurrence of carcinoma of the cervix (41 per cent).

- 2. Deep pelvic recurrences are the recurrences in the lateral parametrium and uterosacral ligaments and in the iliac, hypogastric, or obturator lymph nodes, and are designated as Type B. If the cervix or vaginal vault is also involved, the recurrence is called Type AB (Fig. 2). These made up 41 per cent of the total.
- 3. Cases of bladder and/or rectal involvement are designated as Type C and, if central or deep pelvic recurrences are also present, they receive the additional letter classification of A or B or both (Fig. 3).
- 4. Peripheral pelvic recurrences receive the designation of letter D and imply that cancer is recurrent in the inguinal nodes, pelvic brim nodes, pelvic bones, or lumbosacral vertebrae. If central pelvic or deep pelvic or rectal or bladder recurrences are also present, the appropriate additional letter classification is added (Fig. 4).
- 5. Distant metastases with pelvic recurrence are designated as E and without pelvic recurrences as F.

Recurrence sites and original treatment. Table III summarizes the various sites of recurrence related to the original stage and original methods of treatment. Adequate radiation varied in technique during the 17 years encompassed in this study but for the most part included approximately 5,000 to 6,000 mg. hr. of radium administered to the cervix most frequently with the Corscaden

applicator and supplemented with conventional deep x-ray therapy to 4 or 6 pelvic portals. A few patients received supervoltage therapy. Adequate operation consisted of a radical hysterectomy and pelvic node dissection. Where extrauterine cancer was found, the patients operated upon received deep x-ray therapy postoperatively, either with conventional or with supervoltage machines.

It is evident that the most common sites of recurrence in this series were the deep pelvic tissues, that is, the parametrium and the uterosacral ligaments and, to a lesser extent, the deep pelvic lymph nodes. Either alone or in combination with other sites (A,

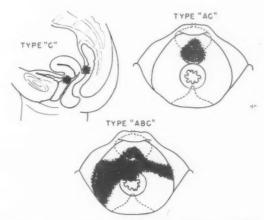


Fig. 3. Recurrences involving the bladder and/or rectum (13 per cent).

Table III. Chart showing recurrence sites in relation to primary stage and primary therapy (all cases)

								Rec	Recurrent si	sites						
			Central	Deep pelvic	pelvic	Bla	Bladder and/or rectal	ler and/or rec	tal		Peri	eripheral pelvic	elvic		Dist	Distant
Imary			-	-	-				-				-	-		
stage	Primary treatment	Total	Y	В	BA	2	AC	AC BC	ABC	D	AD	BD	BD ABD	BCD	E	F

Epidermoid carcinoma

	Adequate operation	14	2	4	1	1		1		- 33	_				- 2	
		100%	14%	35%			14	14%				21%			14%	2
I	Adequate radiation	48	15	19	2	1		2	1	3					2	01
		100%	31%	43%	6		88	8%				9/9			8%	9
	Inadequate operation	8	1	1	2				1			2	_			-
	with/without radia- tion	100%	12%	37%			12	12%				25%			12%	,0
	Adequate operation	20	2	5	2	1			2	2	_	_		_	7	2
П		100%	10%	35%			15	15%				10%			30%	10
	Adequate radiation	61	8	16	12				5	4	-	2	-		9	7
		100%	13%	45%			8	8%				11%			21%	0
Total I's and II's	s,II pu	151	28	45	19	3		3	6	12	-	4	1		14	12
		100%	19%	42%			6	9%6				11%			17%	0
and re-	III and re- All types of treatment 72	72	11	13	17	3	2	4	80	-	1		-	1	7	+
CHEFFICE		100%	15%	41%			24	24%				5%			15%	10

Adenocarcinoma

	Operation	5		-				0.	1.						1	01
1		100%		20%	9		20	20%							%09	
	Radiation	12	4	1	3					1		1			-	1
		100%	33%	33%	9/							17%			17%	
	Radiation	10		3	2					1					2	2
II and III		100%		50%	10							10%			40%	i
		250	43	63	41	9	2	7	18	15	1	5	2	1	25	21
Full total		100%	17%	419%	14		13	13%				10%			Inter	

Fig.

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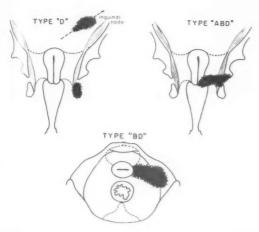


Fig. 4. Peripheral pelvic type of recurrence (10 per cent).

C, D, E) the deep pelvic tissues were involved in almost 60 per cent of the recurrences, while the central pelvic tissues alone were involved only 17 per cent of the time. If one adds to this large group of deep pelvic recurrences those with distant and peripheral pelvic recurrences, the cases amenable to retreatment with cure as the objective are very few.

These figures also suggest that the weak spot both in radiation therapy of primary disease and in the radical surgical excision of the primary lesion is at the periphery of the therapeutic fields and that each modality fails most frequently to destroy or remove all the malignant cells in these deep pelvic tissues.

As one would expect, since radical operation removes the cervix, the primary site of disease, cases of central pelvic recurrence were less frequent following operation than after irradiation.

In 143 Stage I and II cases of recurrence originally treated either by adequate radiation or by adequate operation there were almost twice as many patients with central pelvic recurrences after radiation as after operation but fewer with distant metastases after radiation than after operation. These findings are summarized in Table IV.

Truelson's¹³ large series of 704 cases shows a similar high rate of recurrence in the deep

pelvic tissues (54 per cent) but a higher central pelvic recurrence incidence than ours (40 per cent). Kottmeier's figures for these sites of recurrence are 43 per cent deep pelvic and 32 per cent central. Both these series are almost entirely radiation cases.

The diagnosis of recurrence

Initial symptoms and signs. The majority of patients were not aware that a recurrence was present and had no symptoms, the disease being detected by physical examination of the pelvis. The first symptom of recurrence most commonly was pain, usually in the lower back, the hip, or the pelvis, with

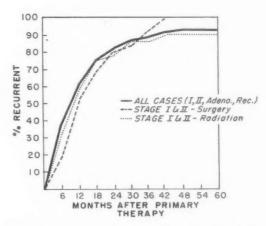


Fig. 5. Time of recurrence of carcinoma of the cervix.

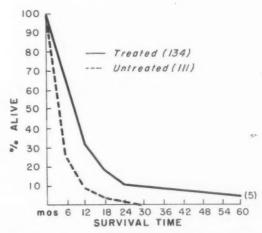


Fig. 6. Survival time after treatment of recurrence of carcinoma of cervix compared with survival time with no treatment (all cases).

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Table IV. Chart showing recurrence sites in relation to primary stage and primary therapy (143 Stage I and II cases only)

	Total		Central pelvic A		Deep pelvic B-BA		Bladder, rec- tum involved C-BC- AC-ABC		Peripheral pelvic D-AD-BD ABD-BCD		Distant E-F	
Original treatment	No.	%	No.	%	No.	%	No.	1 %	No.	1 %	No.	1 %
Adequate opera- tion	34	100	4	12	12	35	5	15	5	15	8	17
Adequate radia- tion	109	100	23	21	49	45	9	8	10	9	17	16

Table V. First symptom of recurrence in carcinoma of the cervix

First symptom of recurrence	Total	Central (A)	Deep pelvic (B-AB)	Bladder, rec- tal involve- ment (C-AC-BC- ABC)	Peripheral pelvic (D-AD- BCD)	Distal (E-F)
None	101	31	50	9	2	9
Pain	76	5	35	11	12	13
Bleeding	26	8	. 9	5	3	1
Obstructive uropathy	25	2 .	8	7	3	5
Edema	13	1	5	-	3	4
Other*	16		2	1	1	12

*Intestinal obstruction 3; anorexia 2; rectovaginal fistula 1; dyspnea 2; cough 8.

or without radiation down the leg. Bleeding was the first symptom in only 10 per cent of cases, as would be expected with the relatively small number of central pelvic recurrences.

Although obstructive uropathy was the

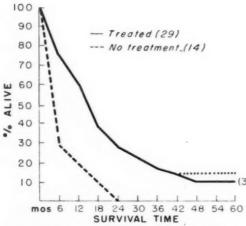


Fig. 7. Survival time in Type A, central pelvic type of recurrences, after treatment and with no treatment.

initial diagnostic evidence of recurrence in only 10 per cent of the cases, when intravenous pyelography was employed it showed obstructive uropathy 90 per cent of the time. Pearson¹¹ found obstructive uropathy in 75 per cent of his cases of cancer of the cervix. This is also in keeping with the high incidence of deep pelvic recurrences. The ureteral obstruction was most commonly very close to the bladder or in the terminal ureter.

The high incidence of obstructive uropathy suggests that intravenous pyelography is probably the earliest and most sensitive indication of recurrence and that it ought to be performed frequently in the follow-up. An abnormal intravenous pyelogram must be considered evidence of recurrence until proved otherwise.

Edema was the presenting symptom of recurrence in 5 per cent of the recurrent cases. Table V summarizes the first symptoms of recurrence. Love's cases had a much higher incidence of bleeding than did ours.

Interval between primary therapy and re-

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currence. Sixty per cent of recurrences were first evident within one year after completion of the initial therapy and by 21/2 years between 85 and 90 per cent of the recurrences had appeared. Fig. 5 summarizes the time interval between primary therapy and recurrence. There were 17 recurrences that did not appear until long after 5 years had passed; these cases had all been treated with primary radiation therapy. All recurrences after radical operation were found within 3½ years. The obvious inference is that with radical operation if a patient has no recurrence by 3½ years, she is permanently cured but after radiation therapy even 5 years is not long enough to be sure of cure. Van Herik¹⁴ reported 80 per cent of recurrences within 24 months and 3.6 per cent recurrences after 5 years. Truelson13 found 86 per cent within 24 months and 1.2 per cent after 5 years.

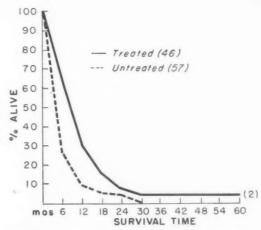


Fig. 8. Survival time in Type B, AB, deep pelvic recurrences after treatment and with no treatment.

The management of recurrences

Table VI summarizes the management of the 250 recurrent cases in this series. The 5

Table VI. Methods of treatment of recurrences in this series

Type of recurrence	Treatment of recurrence	Number	5 year survivals
A (central pelvic)	Exenteration	1	
	Exenteration plus supervoltage x-ray	1	
	Radical hysterectomy plus node dis-		
	section	9	1 (really 3½ years)
	Radical hysterectomy plus node dis-		
	section plus supervoltage	2	
1	Conventional radiotherapy	16	2
	Supervoltage radiotherapy	1	1
	None	13	
B-BA (deep pelvic)	Exenterations	3	
and (deep perio)	Exenterations plus x-ray	1	
	Radical hysterectomy plus node dis-	-	
	section	4	1
	Total abdominal hysterectomy plus		
	x-ray	1	
	Conventional radiotherapy	28	
	Supervoltage radiotherapy	10	
	Local excision (node)	1	1
	Urinary diversions	6	
	None	51	
C-AC-BC-ABC (rectal and/or	Exenterations	12	42
bladder involvement)	Exenteration plus supervoltage		
mudel involvement)	Conventional radiotherapy	2 2	
	Supervoltage radiotherapy	6	
	None or inadequate (!)	12	
DED ADD AD E E (mainham)	* ' '		
D-BD-ABD-AD-E-F (peripheral	Conventional radiotherapy Supervoltage radiotherapy	28 6	
privic or distant)	Bowel surgery plus lung radiotherapy	1	
	Palliative bowel surgery	2	
	Urinary diversion	1	
4	None	30	
	MOHE	30	

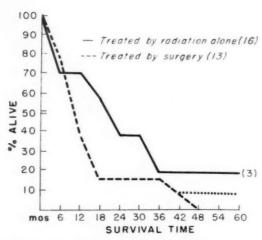


Fig. 9. Survival time in Type A, central pelvic type of recurrences treated, 16 by radiation, 13 by operation.

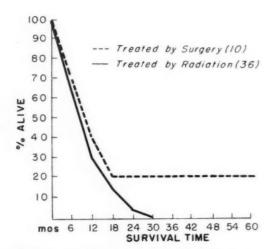


Fig. 10. Survival time in Type A, AB, deep pelvic type of recurrences treated, 10 by operation, 36 by radiation.

year survivors are so few that the first thought on compiling these figures was to examine the figures in order to learn if there is any point at all in treating a recurrence. Fig. 6 was therefore compiled showing the survival curve for all patients, 134 of whom were treated for recurrence and 111 of whom were not. While the difference between the two groups is far from being spectacular, the survival rate of the treated patients was certainly better, for the untreated were all dead within $2\frac{1}{2}$ years.

Fig. 7 shows a distinct difference in the

survival curves of treated versus the untreated central pelvic or Type A recurrent cases where the recurrence was thought to be limited to the cervix and/or vaginal vault. The untreated patients were all dead by 18 months at which time 40 per cent of the treated patients were still living, albeit all but 3 or 4 died within another 2 years. There were, however, 3 five year survivors of the treated patients with Type A or central pelvic recurrences and a fourth patient is living and well at 42 months.

The value of treatment is still evident in the survival curves of the deep pelvic (B-BA) recurrence group (Fig. 8). The margin is a slim one, however, between the treated and untreated groups, and rests entirely on 2 patients cured by operation.

Except for the five 5 year survivors, Figs. 9 and 10 show little or no difference between the survival curves of the central pelvic (A) and deep pelvic (B, AB) recurrences when examined with respect to radiotherapy versus radical operation.

Table VII gives the salient facts about the five 5 year survivors. Three of the cases were central pelvic or Type A recurrences while 2 were deep pelvic recurrences with positive nodes (B, BA).

D. N. had a recurrence in one large obturator node 6½ years after conventional radium and x-ray therapy of a Stage I

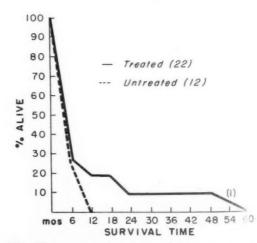


Fig. 11. Survival time in cervical cancer recurrences involving bladder and/or rectum, 22 treated, 12 untreated.

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Fig.

carcinoma in the cervical stump; the node was dissected free from the external iliac arrery and removed with a portion of iliac vem and the patient is still living 7 years later without any further treatment.

L. S. originally had a stump carcinoma of unknown stage treated elsewhere with radium alone. A radical hysterectomy and node dissection were done for recurrence 7 years later in the cervix, vagina, parametria, and one node. This operation was followed by radiotherapy and the patient is still alive 7 years later.

C. D., with a Stage II case, was treated by simple total hysterectomy because of obesity, followed by radiation. When recurrence took place one year later she received radium to the vaginal vault and is still living 9 years later.

C. W. had a radical hysterectomy and pelvic node dissection for a Stage I lesion, which recurred 14 months later; she was treated with massive radiation therapy, part of it with conventional voltage and part with supervoltage. She is alive 9 years later with many radiation complications.

L. M. received additional radium to a Stage I lesion recurrent one year after initial radium and x-ray and survived 8 years before she died, probably of cancer.

Attention must be called to the fact that none of the 5 year survivors underwent an

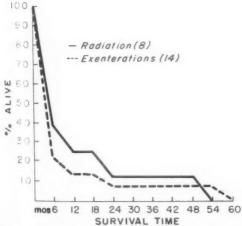


Fig. 12. Survival times in cervical cancer recurrences with bladder and/or rectal involvement, comparing methods of treatment.

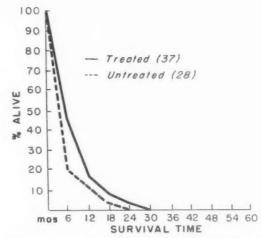


Fig. 13. Survival time in peripheral pelvic and distant recurrences of cancer of the cervix, treated and untreated.

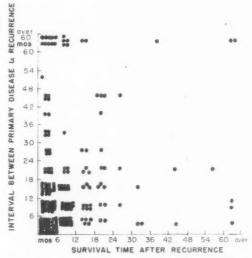


Fig. 14. Relationship of interval between initial treatment and recurrence to survival time after recurrence.

exenterative procedure. Our results with exenterations for recurrent disease have been most unsatisfactory, with the longest survivor living a bedridden 54 months.

Fig. 11 shows that it was still probably of value to treat the patients in this series with recurrent disease even if the bladder or the rectum or both were involved. It must be recognized, however, that one is only prolonging survival time and not curing the disease. Fig. 12 shows that radiation does as well as exenteration in this respect.

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Tab

Table VII. The five 5 year survivors following treatment of recurrent cervical cancer

Patient Age Primary		Primary		Recurr	ence	Treatment of	Years alive with diagnos
			Primary treatment	Interval to	Site of	recurrence	of recurrence
D. N.	54	I-C	4,000 mg. hr. radium Adequate conventional x-ray	6½ years	B (node)	Local excision of obturator node	7 years
L. S.	55	? Stump	Radium alone else- where	7 years	BA (prox.)	Radical hysterec- tomy, node dis- section, conven- tional x-ray	7 years*
C. D.	54	П	Total abdominal hys- terectomy, bilateral salpingo-oophorec- tomy + conventional x-ray	1 year	A	Radium	9 years
C. W.	31	I	Radical hysterectomy + node dissection (neg.)	14 months	A	3,200 r TD 250 kv. 4,100 r TD 2,000 kv. 3,000 r TD 180	9 years
						kv.	
L. M.	34	I	5,000 mg. hr. radium Adequate conventional x-ray	1 year	A	5,800 mg. hr. radium includ- ing needles	8 years (dead now?)

*Pathology report carcinoma in cervix, vagina, 1 node and parametrium.

Fig. 13 deals with cases of recurrence in the pelvic bones, inguinal nodes, and distant organs. There was very little difference in this group in the survival curves of the treated versus the untreated patients, casting doubt on the value of any treatment for recurrences of these types except for relief of pain.

Thus, in summary, the value of the treatment of recurrences is sharply limited. Central pelvic recurrences should be treated not only to prolong survival time but possibly also to achieve an occasional cure. The same may be said for deep pelvic recurrences but not so strongly. When bladder or rectum became involved, the best that treatment offered was slight prolongation of survival time. And when pelvic bone, inguinal nodes, extrapelvic nodes, or distant organs became involved, treatment was of no value.

The inaccuracy of clinical evaluation of extent of recurrence. Management of recurrence is rendered difficult and frustrating by the fact that clinical evaluation of just how far the recurrence has spread is highly inaccurate when compared with autopsy proof

of extent of disease. Table VIII shows the gross failure of correlation of extent of disease in 74 autopsies comparing clinical evaluation of extent of disease with actual proof of extent of disease. To be sure, an average of 6.1 months elapsed in these 74 cases between clinical diagnosis of extent of recurrence and autopsy, but the fact that at autopsy 58 of the 74 had distant metastases, whereas 6 months before only 21 were thought to have distant metastases, shows how unwarrantedly overoptimistic were most initial diagnoses of recurrence. Henriksen⁶ and de Alvarez4 pointed out a 20 per cent error in the clinical diagnosis of extent of disease when compared with autopsy findings.

Table IX summarizes the various sites of metastases under two headings, first, based upon clinical evaluation in 250 cases, and, second, based on autopsy findings in 74 cases.

Speed of recurrence and survival. Fig. 14 is a scattergraph relating speed of recurrence to survival time after recurrence. It shows that the great majority of cases recur within

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Table VIII. Correlation of clinical diagnosis of extent of recurrence with autopsy proof of actual extent of disease

Clinical diag- nosis of extent		Autopsy proof of actual extent of disease										No disease	
of disease	Total	A	В	C	BCD	AC	AB	D	ABD	ABC	E	F	P Rx
A	10						1			1	5	3	
В	13		1					1		2	6		3
C	3									1	2		
BCD	1										1		
AD	1										1		
AB	11					1				1	7	2	
BC	3			1							1		1
ABD	2										2		
ABC	7										5	1	1
E	12										11	1	
F	9										1	8	
No disease	1										1		

Table IX. Summary of sites of metastases

		ation of extent (250 cases)	Autopsy proc of disease (
	Total	%	Total	%	
Cervix	69	27	10	14	
Vagina	98	38	15	20	
Ovary	2	1	7	9	
Parametria	158	62	34	46	
Pelvic nodes	27	11	12	16	
Bladder	30	12	25	34	
Rectum	17	7	13	18	
Ureters	3	1	20	27	
Inguinal nodes	12	5	3	4	
Bony pelvis and sacral vertebrae	12	5	9	12	
Psoas muscles	1	0.5	2	3	
Vulva	1	0.5	4	5	
Other bones	8	3	15	20	
Paraaortic nodes	10	4	16	22	
Peritoneum	5	2	7	9	
Bowel	9	4	20	27	
Liver	7	3	21	28	
Omentum	4	2	1	1	
Lungs and pleura	19	7	29	39	
Mediastinum	2	1	13	18	
Heart			5	6	
Neck nodes	4	2	2	3	
Thyroid			4	5	
Brain			1.0	1	
Skull			1	1	
Skin and abdominal wall			6	8	
Diaphragm			2	3	
lliac vessels			4	5	
Kidney			7	9	
Adrenal			6	8	
Pancreas			3	4	
Spleen			3	4	
Spinal cord	1	0.5			
Pituitary		0.0	1	1	
Breast			1	1	
Inferior vena cava			1	1	
No tumor			4	5	

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18 months and death ensues within another 18 months. Patients with late recurrence will die just as soon as will those with early recurrence, however.

Comment

The extremely unhappy end results in this series of recurrent carcinomas of the cervix lead us to a few conclusions.

First, as a critique of present methods of treating primary carcinoma of the cervix, the great preponderance of recurrences take place in the lateral deep pelvic tissues, the parametria, and uterosacral ligamentsthose areas specified as B in our classification. This makes it evident that both radiation and radical surgery frequently fail here at the periphery of the treated fields to destroy all of the cancer, even though pathology specimens at the time of primary therapy suggest that the peripheral field has been adequately treated. This principle is not new and for years radiation therapists and surgeons have been attempting to increase the peripheral tumor dose of radiation or to make the peripheral surgical dissection more complete. Obviously, were there a good method of determining the true periphery of a given cancer the therapist's job would be greatly facilitated.

As to the proper method of treating recurrent cervical cancer, this would vary with the type of recurrence. Patients with central recurrences following primary radiotherapy seem best treated by radical hysterectomy and node dissection although sometimes repeat radiation may be preferable. Patients with recurrence following operation for primary disease are usually treated with radiation.

It is frequently most difficult to decide whether further treatment is of any value whatsoever even as a palliative, merely life-prolonging procedure. We have tried in this series to answer this latter question. Our poor results with exenterations for recurrent carcinoma, i.e., no 5 year survivors treated in this manner, are at variance with the experience of others^{1, 10, 12} who have salvaged some patients with recurrence by this oper-

ation, reporting 10 to 20 per cent successin selected series.

Certainly the diagnosis of recurrence can be made much earlier by the frequent use of intravenous pyelography and it is suggested that this be done at least every 6 months for the first 2½ years after completion of primary therapy. Any abnormality in the pyelogram should create suspicion of recurrence and determination thereafter of the presence or absence of recurrent cancer should be vigorously sought.

Summary

- 1. Of 250 patients with recurrences of all types of cervical cancer only 5 were salvaged.
- 2. Survival curves show it to be of value to treat patients with central pelvic recurrence and possibly some with deep pelvic recurrence both with respect to increased survival time and also to cure.
- 3. Patients with rectal and bladder involvement had a slightly increased survival time with treatment but no cures were obtained.
- 4. It is pointless (with present methods of therapy) to treat patients with distant spread or peripheral pelvic spread.
- 5. The significance of metastases in special sites is analyzed and the failure of clinical methods to locate recurrences accurately is emphasized.
- 6. The most common site of recurrence is in the deep pelvic tissues, i.e., the parametria and uterosacral ligaments. It is evident that methods of primary treatment should be reexamined with respect to their effectiveness in treating these areas.

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Discussion

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Dr. Frank R. Smith, New York, New York. Drs. Munnell and Bonney have presented the results of their study of 250 patients with so-called recurrent carcinoma of the cervix at Sloane Hospital for Women and at Francis Delafield Hospital. Their study was aimed at the when, why, and where the disease recurs, the therapies used, and the salvage rate obtained. This report is not suitable for comparison with statistical reports from other clinics because of the basic differences in the criteria of selection and differences in methods of therapy.

After reiterating the admitted truth that the stage of the disease is still the most important prognostic factor, the authors conclude that it is of value to treat central pelvic and possibly some deep pelvic recurrences, but pointless to treat patients with distant or with peripheral spread.

There were no cures of recurrences by exenteration in this series, yet other clinics have reported 5 year salvage of from 15 to 23.5 per cent. Since these percentage figures included some primary cases, the obvious inference is the necessity for more radical therapy as the primary and most effective therapy. The survival of only 5 patients out of 250 in 5 years is not very encouraging for the program of therapy used. "Too little and too late" still explains many failures with the present available modalities.

The incidence of 9 per cent ovarian involvement at autopsy brings interesting information. While it adds confusion to, it does not condemn, the theory of Milton McCall that in early stages of carcinoma of the cervix in young women one or both ovaries may be conserved without altering the prognosis.

1) R. MICHAEL J. JORDAN, New York, New York. Dr. Munnell's excellent presentation emphasizes the need for earlier diagnosis and more adequate primary therapy in the treatment of carcinoma of the cervix. The over-all accuracy of present-day cytologic reporting is well over 90 per cent and at the Strang Clinic of Memorial Center is estimated to be over 98 per cent. Since

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the introduction of routine cytologic study at Strang Clinic over sixty thousand women have been screened. Of this group about 50 per cent return annually and in this return group 45 cases of carcinoma in situ have been detected. During the same period of time no invasive carcinomas have been reported. Thus one can state almost unequivocally that carcinoma of the cervix is a preventable disease.

The early diagnosis of recurrent carcinoma after either irradiation or operation, unless it be in the vaginal vault, is almost impossible without laparotomy. Once adequate irradiation has failed there is no place for reirradiation and the patient should be given the benefit of operation. While initially instituted as palliation, a sufficient number of patients are alive and well 5 to 10 years following radical surgery for this modality to be considered curative rather than palliative or experimental.

A review of 493 patients with recurrences admitted to the Gynecological Service of Memorial Center since the institution of the radical surgical program by Brunschwig reveals that 268 (54 per cent) were deemed operable with a 5 year survival rate of 20.5 per cent.

In the irradiation-failure group cases residual or recurrent within 6 months following therapy have a far worse prognosis than those which recur more than 6 months after treatment. One must consider two factors, inadequate irradiation and irradiation resistance.

The results of surgery for recurrent disease following previous operation will depend on several factors. One must state that it might not be necessary at all had the initial surgery been competent. The location of the lesion, i.e., at point A versus points B, C, etc., is important, since the farther away the recurrence is from point A, the more radical is the surgery required.

Before performing initial radical hysterectomy one should consider carefully the extent of the lesion—whether it involves bladder or rectum because it is this group of cases that are particularly amenable to anterior, posterior, or total initial exenteration.

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In summary, when we consider the time and effort which must be expended in doing radical and ultraradical surgery in order to salvage 20.5 per cent of 268 cases and then consider the over 80 per cent salvage in Stage I lesions and the 100 per cent survival rate in carcinoma in situ, we become more aware of the fact that the answer rests in greater emphasis on early diagnosis and detection.

Dr. Langdon Parsons, Boston, Massachusetts. I would like to comment on Dr. Munnell's paper because things are not quite as gloomy for secondary treatment of carcinoma of the cervix as would appear in the series he presented. The primary point is that the time to treat this disease properly is the first time you see it. None of us is very happy about trying to follow up with secondary treatment and that is true whether it is radiation or surgery. This emphasizes the need for more concentrated effort at the time we originally see the patient and outline our treatment for the primary disease of carcinoma of the cervix, which is a local disease, in my mind.

Dr. Jordan has said cancer of the cervix is preventable, and I would almost put it in the class of curable with, of course, many reservations. It seems to me that in our primary treatment we are concentrating far too much on the lateral extensions of the disease and not enough on the primary tumor. I think it is important to do a node dissection, and I think, in Stage I cases, we will be able to salvage a certain percentage of that group but we will not be able to do it unless the primary treatment of the local disease is adequate. I think that is true whether you employ surgery or radiation.

Secondary irradiation is certainly most unsatisfactory, particularly when the original treatment has been adequate. Such irradiation is most likely to make the patient miserable without improving the end results. Operation on the other hand does have something to offer to the patient who has not been cured by the original irradiation. It is true that I am talking about a selected group of cases, for if there is evidence of spread to a distal area there will be little point in carrying out a radical surgical attack.

We find it very difficult to stage carcinoma of the cervix accurately following heavy irradiation. Actually you cannot tell how much disease there is until you perform an exploratory operation. We have found that the disease has spread much more in the fore and aft directions than we ever believed before and that in many cases even in irradiation or surgical failures, the node are involved surprisingly infrequently. It is true that approximately 40 per cent of this group will have positive nodes but this is far less than you might expect. There is still a pronounced tendency of the career of the disease to remain local. For that reason we have attempted in our surgical approach to tailor the type and extent of surgery to the amount of the disease the patient has.

I can report on only 80 cases where operation was done for irradiation failure 5 or more years ago. In approximately 20 of the 80 cases we were able to do Wertheim operations with node dissection. It is rather surprising that the patients still had their disease so confined that a Wertheim procedure could be considered adequate. In the remaining 60 cases an exenteration procedure of one type or another was performed. In the Wertheim group the 5 year salvage was 65 per cent, including 4 of 9 who had positive nodes. Where the nodes were negative the salvage is up around 80 per cent. On the other hand, only 20 per cent survived when exenteration procedures were done. None who had positive nodes in this group lived 5 years. Considering the two groups, the total salvage at 5 years in this group of 80 patients where operation was performed for irradiation failure was 35 per cent.

There is still hope of salvage when irradiation has failed. It is far better, however, to concentrate on the initial therapy in the hope of achieving a primary cure.

DR. MUNNELL (Closing). As Dr. Smith pointed out, it is difficult for us to compare our series of recurrences with those of others reported in the literature. We have tried to eliminate the factor of selection, attempting to figure out how bad the situation is once the carcinoma does recur in all cases and not just in selected cases.

Our 5 year cures with exenteration occurred only in cases of primary disease. Some feel these figures suggest a more and more aggressive policy during the period of follow-up, aggressive from the point of view of diagnosis with perhaps more frequent exploratory operations, if only to prove or disprove the question of whether ecurrence has taken place.

The importance of early diagnosis and of adequate initial treatment of the primary disease has been emphasized again and again this morning by all the discussers. We heartily concur.

Sigmoidovaginostomy: a new method of obtaining satisfactory vaginal depth

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IN THE treatment of malignant disease of the cervix, as in the treatment of any invasive cancer, the first and overwhelming consideration is a program that offers the patient the best prognosis. This does not necessarily mean the greatest chance of remaining alive for an indefinite length of time, for there are obvious situations of chronic invalidism and lingering terminal illness that are not desired by or tolerable to some patients. Therefore, the choice of treatment must be tempered by the likelihood of effecting a cure in a given situation, by the age and health of the patient, by the patient's desire to live under circumstances that are not entirely normal, and finally, by the complications that may result from treatment.

In the treatment of cancer of the cervix, the weapons that are available include all forms of irradiation as well as formidable and destructive operations. As a result of the availability of supportive measures, such as blood, fluids, and antibiotics, and, with some understanding of the response of tissues to various forms of treatment, it is possible to keep the initial loss of life at a minimum; and the over-all prognosis has gradually increased. But as the salvage rate of the more

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advanced cases of cancer has improved, other difficulties have been encountered, such as all types of fistulas; the need for colostomies and diversions of the urinary tract into the colon or to artificial bladders formed of loops of bowel or skin (ureterostomy); loss of ovarian function and resultant menopausal symptoms; and, finally, as a result of destruction of tissue by treatment or of changes in tissues due to inflammation or fistulas, loss of the vagina as a physiologic organ. It is the last facet that is the subject of this paper, together with a proposed method of restoring the vaginal tract to a more normal physiologic structure, one that will permit coitus that is satisfactory to both partners.

This is not a new problem, and although earlier investigators wrote papers dealing primarily with congenital absence of the vagina and proposals for its reconstruction, they were also concerned with loss of the vagina by an occasional postpartum slough. Dupuyten,1 in 1817, dissected a tract between the bladder and the rectum for congenital absence of the vagina, but the tract could not be kept open satisfactorily. Many types of obturators have been utilized in an effort to keep the vaginal tract patent, with varying degrees of success. Methods for the treatment of congenital absence of the vagina now vary from Frank's method2 of gradually increasing the size of an obturator utilized by the patient herself, to the use of all forms of labial, pediculated, or free grafts. The latter methods, as favored by McIndoe3 and by Counseller and Flor,4 have been satisfactory and have rarely been associated with death; however, they require prolonged use

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The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Presented at the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960.

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of obturators, and there is always a tendency for the vagina to contract. Theoretically, the use of an intestinal transplant would be preferable in that there would be a cavity lined with mucous membrane—the grafts mentioned form a cavity lined by skin—with little tendency toward contraction, and such a cavity could be constructed to any length. However, any operation required for the isolation of such a segment carries a definite risk, and only in recent years, with the availability of antibiotics, have such operations become fairly safe.

Snegireff.⁵ in 1892, was the first to utilize the rectum in constructing a vagina. His method was modified and improved by Popow, in 1910, and by Schubert, in 1911. The newer methods consisted of removing the coccyx, retroperitoneally resecting the lower 12 cm. of rectum, transplanting this segment forward to form a vaginal tract, and then pulling the upper portion of the rectum down to or through the anal sphincter. Baldwin,8 in 1904, discussed a patient with a postpartum slough of the vagina. Having opened the vagina and packed it with gauze to furnish a path for the menstrual blood, he then proposed to isolate a loop of sigmoid and to re-establish the continuity of the sigmoid by a primary anastomosis. He planned to draw the double loop of isolated sigmoid into the vaginal tract, one end to be closed and one end to be sutured about the cervix; the middle part of the loop was to be opened and sutured to the labia. After 2 weeks the septum between the loops was to be crushed to produce a single cavity. Unfortunately, the patient failed to return for the proposed operation.

In 1907, Baldwin⁹ reported a variation of this technique in which he used an isolated double loop of ileum in a manner similar to that proposed for the sigmoid in 1904. He reported good results in a single case. Mori, ¹⁰ in 1910, tried using a single loop of ileum as a modification. Masson, ¹¹ in 1940, reported that after 10 successful cases in which Baldwin's operation was used with no death ensuing, 2 of the next 4 patients died, giving an over-all mortality rate of 14 per cent.

Wagner¹² had successfully used an isolated section of sigmoid to anastomose the cervisto the lower part of the vagina in a patien with atresia, and he had re-established the continuity of the sigmoid per primam. Interestingly, the patient was later delivered of a healthy infant through this portion of bowel.

Schubert,⁷ who in 1911 modified the operation for the use of the rectum in the formation of an artificial vagina, wrote a paper in 1932 on the construction of a new vagina with the sigmoid; he included a remarkably complete review of the literature to that time.

Only occasional case reports have appeared in the English and French literature, such as that of Masson. In 1952, Schmid reported on 10 patients he had treated, from 1947 to 1952, in whom the sigmoid was utilized to form a vagina; the mortality rate was low, there were few complications, and results were good.

The greatest interest in the use of bowel to construct a vagina has been shown by the Russians. Alexandrow, 15 in 1942, reported the subsequent pregnancy and delivery of a healthy infant by cesarean section after reconstruction of a vagina with a loop of sigmoid. He had performed the operation 67 times, with a mortality rate of 2.9 per cent. Gigovskij, 16 in 1956, reported a total of 110 cases in which the sigmoid was utilized, with death resulting in one case. He re-established the continuity of the bowel immediately with an end-to-end anastomosis and then pulled the distal end of the isolated segment of sigmoid to the introitus. The inner end was closed and extraperitonized beneath the peritoneum of the cul-de-sac. Finally, Alexandrow, 17 in 1955, published a monograph, with photographs, charts, and diagrams, of his method of utilizing the sigmoid in the construction of a vagina. He recorded his results in 175 cases, reporting a mortality rate of 17 per cent, and provided an excellent bibliog-

In all of these papers the emphasis is on the treatment of congenital absence of the vagina and not on reconstruction of a vagina. Interest in the latter problem is previlent, however, and occasionally a paper appears, such as that of Simmons, 18 who reported coital function in a patient by means of an epithelized perineal tract after she had undergone pelvic exenteration.

Webb and associates,19 in 1954, made a specific and tremendous effort to restore vaginal function in a patient with carcinoma of the cervix treated by irradiation, in whom recurrences had made exenteration necessary. Subsequently, because of infection of the upper part of the urinary tract, they constructed a cecal bladder for the urine and brought a second segment of ileum to the introitus to re-form the vagina. An ileotransverse colostomy re-established the continuity of the bowel to the sigmoid stoma. In the discussion of the case, these authors stated that little could be found in the literature about the problems of reconstructing a vagina after destructive opera-

The operation to be described in this paper is the result of the experience with a patient with postirradiation carcinoma of the cervix and sigmoidovaginal fistula, whose pertinent question was, "Can my sex:life be helped in any way by this operation?" Her chief difficulty was narrowing and shortening of the vagina; this had developed after treatment for cervical carcinoma. When the abdomen was explored and no distant metastatic lesions were found, we felt justified, with the patient's request in mind, in attempting to gain added depth and width for the vagina in addition to repairing the sigmoidovaginal fistula. When this proved feasible in that particular case, further attempts were made, with modifications and refinements, in a small series of cases. The results have been gratifying from a physiologic as well as a reconstructive viewpoint.

Method

The abdomen is opened through a midline incision, which is extended above the umbilicus if necessary, and the entire abdomen is explored for evidence of extrapelvic extension of the malignant disease. Particular attention is paid to the aortic region, and if

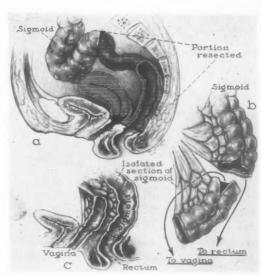


Fig. 1. a, Possible extent of excision of distal portion of sigmoid, rectosigmoid, upper part of rectum, uterus, and a third or half of the vagina. b, Sigmoid divided, showing necessary rotation of isolated segment and antimesenteric split to make opening larger and permit anastomosis of isolated segment to vagina and of sigmoid to rectum. c, Relation of isolated segment of sigmoid to vagina and rectosigmoidostomy.

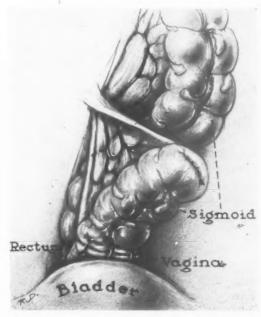


Fig. 2. Schematic representation of the sigmoidovaginostomy, which is normally hidden by the bladder. Most of this segment can be extraperitonized.

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any firm, palpable nodes are encountered, biopsy is performed. If the highest aortic nodes obtainable are involved, the abdomen should be closed as in exploratory laparotomy.

Since the majority of these patients have had squamous cell epithelioma of the cervix, dissection of the iliac and obturator nodes is done next. The ureters are then unroofed and freed from the tissues lateral to the cervix.

If there is a possibility that the malignant disease has recurred in the rectovaginal region, if the rectosigmoid is adherent to a suspicious-appearing lesion, or if a fistula is present and resection of the rectosigmoid and lower part of the sigmoid is contemplated, the sigmoid should be divided between forceps well proximal to the fistula or adherent portion of the bowel and in a region that seems to have little if any reaction to irradiation. Particular care should be taken to preserve the blood supply to the proximal end of the sigmoid. After the branches of the superior hemorrhoidal artery have been divided, a cleavage plane can be developed posteriorly in the hollow of the sacrum until the rectum is freed past the level of the fistula or the recurrent malignant lesion; the rectum can later be transected in healthy bowel. As the surgeon works from posterior to anterior, the connective tissue, usually including the middle hemorrhoidal arteries, is clamped and stick-tied. This procedure gradually frees and mobilizes the rectum and vagina, which are then divided below the lesion; the cervix, uterus, tubes, ovaries, a portion of rectum, the rectosigmoid, and the lower portion of the sigmoid can be removed en bloc (Fig. 1). Bleeding is troublesome from the tissues below the ureters, and considerable oozing also takes place from the edges of the vagina and the pubocervical fascia. A pack is placed temporarily in the pelvis to reduce the loss of blood.

The lateral peritoneal attachments of the sigmoid and descending colon are divided as high as is necessary to allow the surgeon to slide the sigmoid down into the pelvis and bring it to the inner end of the rectum without tension. One frequently finds at this stage that the blood vessels to the sigmoid which extend fanlike from the inferior mesenteric artery, will allow any part of the terminal 6 to 8 cm. of the sigmoid to be brought to the remnant of rectum with ease. It is the utilization of this terminal few centimeters of sigmoid that makes it possible to reconstruct a vagina with minimal additional operation or trauma.

The sigmoid is transected 5 to 10 cm. from its distal end, care being taken to preserve arterial and venous trunks. As little mesentery is mobilized from the bowel as possible in order to preserve the arcades of the vessels. The small, free distal segment of sigmoid must be gently turned back lengthwise on the sigmoid in order to keep this segment out of the way while the continuity of the intestinal tract is re-established (Fig. 2). A satisfactory oblique end-to-end anastomosis can be performed fairly rapidly, even in the deep pelvis, with use of one row of catgut sutures reinforced with interrupted silk sutures.

Because of the minimal separation of mesentery, the small isolated segment necessarily lies reversed and parallel to the sigmoid; it is situated virtually over the sigmoidorectal anastomosis. The proximal end of the isolated segment is therefore adjacent to the open end of the vagina. The diameter of the sigmoidal segment is less than that of the vagina, but, by the splitting of the end of the sigmoidal segment on its antimesenteric border, an oblique end-to-end sigmoidovaginostomy can be performed rapidly with 6 to 8 silk sutures; the ends of the sutures are left extending into the vagina, where they can be removed after several weeks. The distal end of the small isolated segment of sigmoid that forms the new apex of the vagina is inverted on itself with one or two purse-string sutures.

Since three ends of bowel plus the vagina have been open, some minimal contamination of the pelvic peritoneum is inevitable. Because of the contamination and also because of some oozing, it is wise to drain the

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deep pelvis. This can be accomplished with Penrose drains which extend from the vagina through the lateral corners of the sigmoidovaginal anastomosis around the sigmoid to the hollow of the sacrum; the drains may be removed through the vagina in a few days. The pelvis is peritonized and everything except the inner end of new vagina is extraperitonized. If a temporary transverse loop colostomy is performed as a safety factor, the stoma can be closed in 2 to 3 months when the sigmoidorectostomy has healed.

Antibiotics are used postoperatively because of the possibility of contamination during operation. The drains through the walls of the vagina prevent the accumulation of blood, serum, or pus in the pelvis. The patients are allowed up in 24 hours; they are generally out of the hospital as soon as the colon is functioning satisfactorily. Results in the 7 patients are given in Table I.

Report of cases

Case 1. This 30-year-old white married woman was treated at the Mayo Clinic in April, 1957, for a Grade 2, Stage II squamous cell carcinoma of the cervix. The patient received 6,940 mc. of

radium to the cervix and external application of cobalt (Co⁶⁰). After 9 months the caliber of the stools had decreased and a rectovaginal mass had developed. A recurrence of the malignant disease seemed likely.

At exploration in January, 1958, a hard node was found at the bifurcation of the aorta and was removed. Examination of the node revealed a Grade 2 squamous cell epithelioma. The higher nodes were normal. Dissection was begun well up on the aorta, and the lower aortic, common iliac, external iliac, and obturator nodes were dissected and were found to be normal. The mass behind the cervix involved cervix, rectosigmoid, and left ureter. After the rectum was mobilized (with considerable loss of blood), a radical hysterectomy was performed, with removal of adherent bowel, ureter, and upper portion of the vagina; the sigmoid was divided above the region affected by the irradiation. It was found that the proximal portion of sigmoid could be brought to the rectum easily after a distal segment 9 cm. long was isolated. The segment was carefully turned back out of the way. An antimesenteric end-to-end sigmoidovaginostomy was performed, and the distal end of the isolated segment was utilized for an oblique end-to-end sigmoidovaginostomy, for which 6 to 7 silk sutures were used. The left ureter was implanted in the bladder, and a transverse colonic stoma was established. The patient was dismissed

Table I. Results in 7 patients

Patient	Age (years)	Site of ma- lignant lesion	Pre- operative radiation	Preoperative diagnosis	Colostomy required	Blood replaced (c.c.)	Intercourse	Lubricants required
1	30	Cervix	+	(?) Recurrence of carcinoma in vaginal vault	+	5,500	Excellent	-
2	50	Cervix	+	Rectovaginal fistula, ureterovaginal fistula	+	500	Good	-
3	52	Cervix	+	Ulcer of rectum, rectovaginal thickening	+	1,000	Excellent	- ş.
1:	37	Cervix	+	Ulcer of rectum and vagina	600	2,000	Fair	+
5	31	Uterus	+ '	Vesicovaginal fistula	-	1,500	Satisfactory	-
ű	33	Cervix	-	Recurrence of carcinoma	deb	1,500	"For the birds"	+
7	41	None		Sigmoidovaginal fistula	+	1,000	Excellent	-

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on the twentieth postoperative day. The colonic stoma was closed in August, 1958.

In March, 1960, the patient was healthy and had no complaints. Renal function was good. The vagina was smooth and deep, and its apex could not be felt. Intercourse was normal and satisfactory to both partners; no lubricants had been necessary.

Case 2. This 50-year-old white married woman was treated in July, 1957, at the clinic for a Grade 3, Stage II squamous cell epithelioma of the cervix. Treatment consisted of application of 8,000 mc. of radium to the cervix in addition to external irradiation. Nine months later, in April, 1958, she underwent an exploratory operation because of the gradual development of a pelvic mass on the left, and a Wertheim hysterectomy with dissection of the iliac and obturator nodes was performed. No residual carcinoma was found; the nodes were inflammatory. Pronounced changes due to irradiation were visible on the bowel. A left ureteral fistula developed 3 weeks after this operation and a rectovaginal fistula in 6 months, at which time there was also a beginning hydronephrosis on the left side. In October, 1958, the affected region was re-explored, but no metastasis was found. The rectum could be freed for only 1.5 cm. beyond the fistula. A partial resection of the sigmoid was performed, and, after the lateral peritoneal attachments were freed, the middle portion of sigmoid could easily be brought to the end of the rectum. It was possible to divide the bowel 6 to 7 cm. from the end and to retain a good arteriovenous blood supply. By doubling this segment back, an oblique antimesenteric end-toend sigmoidorectostomy could be made. The distal end of the isolated segment was anastomosed obliquely end to end to the vagina with 6 silk sutures. The left ureter was isolated and implanted into a tube made from the dome of the bladder. Finally, a transverse loop colostomy was performed. The patient was dismissed on the fourteenth postoperative day and she returned in January, 1959, at which time the colonic stoma was closed.

In April, 1959, kidney function was good; the vagina was smooth and deep, and its apex could not be felt. Intercourse was said to be possible without lubricants but was not completely satisfactory as yet.

Case 3. This 52-year-old white married woman had been treated elsewhere in May, 1957, for a Grade 3, Stage I squamous cell carcinoma of

the cervix. She was first seen at the clinic in February, 1958, at which time she had an ulcomeasuring 3 by 4 cm. on the rectovaginal wall the lesion was associated with dense thickening that suggested malignancy, although results of biopsy were negative.

At exploration, in February, 1958, the iliac and obturator nodes were removed and were found to be normal. The rectosigmoid showed pronounced changes due to irradiation. The sigmoid was divided at the pelvic brim, and a radical hysterectomy was performed. The resection included the inner third of the vagina, the proximal part of the rectum, the rectosigmoid, and the lower section of the sigmoid. No evidence of recurrent carcinoma was found. The sigmoid was mobilized, and, after a 10 cm. segment was isolated, an oblique end-to-end sigmoidorectostomy and an oblique end-to-end sigmoidovaginostomy were performed. Finally, a loop transverse colostomy was carried out. The patient left the hospital on the twenty-eighth day after operation and returned in June, 1958, at which time the colonic stoma was closed. In April, 1959, the patient's general health was good. The vagina was of normal width and depth, and its apex was barely palpable. Intercourse was "completely satisfactory" to both partners without lubricants, although the patient has spotted on one or two occasions.

Case 4. This 37-year-old white married woman had been treated elsewhere, in September, 1958, for a Grade 3, Stage I squamous cell carcinoma of the cervix. She had received radium and external x-ray treatments. When she was seen at the clinic, in December, 1958, there was no sign of activity, but a small slough was present about the cervix. In October, 1959, back-to-back ulcers 2 by 3 cm. in size were noted in the vagina and rectum at the level of the cervix, and, although biopsies were negative, operation was advised.

In October, 1959, laparotomy was done and did not reveal any distant metastasis. The common iliac, external iliac, and obturator nodes were negative. A radical hysterectomy was performed, including removal, en bloc, of the upper half of the vagina and proximal part of the rectum, including the ulcers, the rectosigmoid, and the lower portion of the sigmoid. After a 7 to 8 cm. section of sigmoid was isolated, an oblique end-to-end sigmoidorectostomy and an oblique end-to-end sigmoidovaginostomy were done, the latter with eight silk sutures. Colostomy

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was not performed. This patient had a perforation of the proximal segment of sigmoid on the posterior aspect above the site of the sigmoidorestostomy. A fistula formed extending from the sigmoid to the hollow of the sacrum and thence into the vagina. This complication necessitated an additional 2 weeks of hospitalization. The fistula has finally closed.

The introitus and labia of this 95 pound woman are atrophic, and although the vagina has good width and normal depth, with the apex beyond the tip of a finger, intercourse is unsatisfactory because of insertional dyspareunia, and lubricants are required.

Case 5. This 31-year-old white unmarried woman was first seen when 26 years old, in 1955. She had been treated elsewhere, in December, 1954, for carcinoma of the cervix; radium and x-ray treatments had been given. There was grayish slough over all of the cervix and vagina, and exploration was advised because of the possibility of radiation-resistant malignant disease. Slides from elsewhere showed the neoplasm to have been a Grade 3 adenocarcinoma. In August, 1955, a Wertheim hysterectomy was performed. The pelvic nodes were removed and were found to be negative. No residual carcinoma was found, but the ovaries proved to be typical Stein-Leventhal ovaries. The base of the bladder was pale and edematous. The patient was advised of the possibility that a fistula would develop.

Four years later, in July, 1959, the base of the bladder perforated. The patient returned to the clinic 48 hours later, and a 2 cm. fistula was repaired transvaginally. The patient was kept face down on a frame for 10 days. However, the entire base of the bladder and most of the vagina sloughed, and the patient was sent home for 4 months to allow the tissue to heal.

In December, 1959, laparotomy was performed. No evidence of nodal or distant metastasis was found. The sigmoid was separated from the back of the bladder, revealing the defect in the posterior wall and in the base; the ureteral orifices were in the edge of the fistula. The trigone was missing. The ureters were dissected back to the pelvic brim in order to remove them from the scar tissue. The sigmoid was divided, an 18 cm. segment was isolated, with its blood supply intact, and the continuity of the bowel was re-established with an oblique end-to-end anastomosis. The isolated segment was transected, and the distal 7 cm. segment was anastomosed to the open inner end of the vagina with a row of silk

sutures. Penrose drains to the pelvis were left at the corners of the anastomosis. The distal end of the remaining segment of sigmoid was split on its antimesenteric border for 5 to 6 cm., opened, and used as a patch on the base of the bladder. Finally, bilateral mucosa-to-mucosa ureterosigmoidostomy was made at the proximal end of this segment of bowel. The patient left the hospital on the fourteenth day after operation. The bladder was functioning, but a 4 mm. vesicovaginal fistula had developed.

In May, 1960, the fistula was uneventfully closed via the vagina. The apex of the vaginal tract could not be reached with the examining finger, and the vagina would admit a bivalvular speculum with ease.

Case 6. This 33-year-old white married woman had experienced 9 days of discomfort after intercourse and was found to have a Grade 3, Stage I squamous cell carcinoma of the cervix. In October, 1958, vaginal hysterectomy and right salpingo-oophorectomy had been performed. One year later, in October, 1959, pelvic examination revealed a firm mass 5 cm. in diameter behind the vaginal vault and adherent to the rectum. Exploration was advised. A needle biopsy performed through the vault confirmed the diagnosis of Grade 3 squamous cell carcinoma, and laparotomy was done immediately. The recurrent tumor involved the vaginal vault and the sigmoid. Bilateral dissection of iliac and obturator nodes was performed, but no metastatic lesions were found. The tumor, upper half of the vagina, and adjacent portion of the sigmoid, rectosigmoid, and rectum were removed en bloc. The proximal portion of the sigmoid was placed in the pelvis after an 8 cm. segment was isolated from the end of the bowel. An oblique end-to-end sigmoidorectostomy was done with one row of catgut sutures and one of silk sutures. The proximal end of the isolated segment was brought to the vault in an oblique end-to-end anastomosis for which 7 silk sutures were used. The pelvis was peritonized cleanly, and drains were left through the vagina to the region of the sigmoidorectostomy. No colostomy was necessary. The patient required emplacement of a Miller-Abbott tube for 5 days but was dismissed on the fifteenth postoperative day. There was troublesome residual urine for another 6 weeks.

In April, 1960, the patient was well. The vagina admitted a full-sized speculum with ease, and the apex of the vaginal vault was beyond reach. The only complication was the develop-

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ment of a few granulations about the silk sutures; these were removed. Subsequently, the patient reported unenthusiastically on coitus although no anatomical difficulties were encountered but lubricants were used.

Case 7. This 41-year-old white married woman had had a transverse loop colonic stoma for 21 years. Colostomy had been necessary when her first childbirth, in 1938, was complicated by a pelvic infection. This had necessitated hysterectomy, which was followed by development of a rectovaginal fistula. Between 1938 and 1942 five attempts were made to close the fistula, but all failed. In 1947, stools again appeared in the vagina, and a second colonic stoma was established.

When seen at the clinic, in August, 1959, the patient, who was 5 feet, 2 inches in height, weighed 200 pounds. There were two colonic stomas on the abdomen, and the rectovaginal fistula was still present. The vagina was shortened, and the patient was experiencing moderate dyspareunia.

On a 1,000 calorie diet the patient lost 55 pounds and returned for operation in January, 1960. At laparotomy filmy adhesions were freed from the entire small intestine. The sigmoid, from the sigmoidal stoma to the fistula, had an outside diameter of 1 cm., and therefore the distal half of the sigmoid and the rectosigmoid, including the fistula, were removed. Four centimeters of vagina remained. The rectum was relatively normal beyond the fistula. The descending colon was freed beyond the splenic flexure, allowing the proximal portion of sigmoid, which was 1.5 cm. in outside diameter, to be brought to the rectum. After a distal segment of 5 to 6 cm. was isolated, an oblique end-to-end sigmoidorectostomy was performed. The isolated segment, however, had such a small diameter that it was necessary to split it longitudinally on its antimesenteric border and to suture both ends to the open vagina; 6 silk sutures were used for this procedure. The pelvis was drained through the vagina. All anastomoses were left extraperitoneal. The patient was dismissed on the tenth postoperative day with instructions to inject an ounce of Metamucil and water into the distal limb of the colonic stoma each day for the purpose of stimulating the bowel to return to normal size. In 3 months the colonic stoma was closed, and at that time the vagina was found to be of average length.

The patient reported in May, 1960, that the

bowel functioned normally. Her weight was 1.55 pounds and was stable. Intercourse was satisficatory to both partners for the first time in years, and no lubricants were necessary.

Comment

The average age of patients with carcinoma of the cervix is between 45 and 50 years, but many are in their 30's or even their 20's. Particularly in these younger patients whose husbands are sexually vigorous there is not only a desire but often a need for the ability to have coitus normally and satisfactorily. Not infrequently, after irradiation or operation, and commonly when both forms of treatment have been employed. there is a loss of vaginal depth and mobility. In the past we have tried molds or packs left in the vaginal tract after operation, but these were not particularly successful measures. When performing a Wertheim hysterectomy we now routinely leave the vaginal vault open, suture the peritoneum of the cul-de-sac and posterior portion of the bladder to the edges of the open vault to cover the raw surfaces, and then loop the sigmoid forward to the back of the bladder to obliterate the opening. In effect, this utilizes a pouch of peritoneum of the cul-de-sac to add to the effective depth of the vagina. If a patient can be encouraged to have intercourse in a matter of weeks, a satisfactory vagina will often result. However, the initial response of many patients to such a suggestion is often a recalcitrant one.

It was the result of trying various methods of obtaining vaginal depth postoperatively that led to the attempt at anastomosing segments of bowel onto the vagina. Our chief interest was to rehabilitate the patient if it was possible to do so without increasing the risk of major complications. Except for scattered reports in the literature, such as that of Webb and associates, 19 there has been little discussion about the possibility of aiding these patients at the time a major operative procedure is being carried out.

The method described is particularly applicable when complications have caused strictures of the rectosigmoid or sigmoid,

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when a rectovaginal fistula is present, when ulcerations occur that predispose the bowel to fistula formation, or when recurrence of a malignant process involves the bowel. In such patients the bowel will have to be transected in any case, and the isolation of a segment for anastomosis to the vagina does not involve a totally new set of surgical circumstances or possibilities for complications; it requires only a realignment and reutilization of tissues that must be handled anyway. Of the 7 cases reported herein, it was necessary to resect the bowel because of rectovaginal fistula in 2 patients and because of ulceration of the rectovaginal septum in 2 others; in another patient it was necessary to obtain tissue in order to patch a hole in the bladder. Needless to say, such surgical procedures are contraindicated if the malignant

lesion has metastasized and is inoperable.

When it is necessary to excise part of the lower portion of the colon, it is relatively easy in most patients with an average sigmoid to isolate the distal 6 to 10 cm. from the proximal end of the bowel and to utilize the segment in the described manner. This segment of bowel must be treated gently in order that its blood supply may be preserved, and, since there is minimal separation of its end from the end of the sigmoid proper, it is not a simple matter to anastomose sigmoid to rectum. Because there is minimal mobility, one must anastomose the proximal end of this isolated portion of bowel to the back of the vagina, but, since no strain will traumatize this site of anastomosis for some time, 6 to 8 silk sutures are sufficient to hold the connection. The inner, or distal, end is closed with purse-string sutures in order to obtain a clean serosal surface, and as much of the anastomosis as possible is extraperitonized. The deeper portion of the pelvis and the hollow of the sacrum can be satisfactorily drained extraperitoneally through the vaginal tract.

In all patients of this series, the sigmoid was the organ chosen for the reconstruction procedure. That this was the best choice of tissue was indicated by Alexandrow's¹⁷ experience with the use of the sigmoid in 175

patients with congenital absence of the vagina. The sigmoid is most suitable because: (1) there is a minimal amount of mucus, and this is relatively nonirritating; (2) the sigmoid is thick-walled and large in diameter compared with the ileum, and therefore it traumatizes less easily and is less likely to undergo stricture; and (3) abdominal pain after intercourse is infrequent when the sigmoid is transplanted whereas Alexandrow¹⁷ reported that pain was frequent when the ileum was used.

No complications directly referable to the sigmoidovaginostomy occurred in these patients other than formation of granulations about the silk sutures. However, the patients required hospitalization for 10 to 28 days; one patient required use of a Foley catheter for 6 weeks at home, one had a perforation of the sigmoidal wall proximal to the sigmoidorectostomy, and one had a vesicovaginal fistula in spite of the fact that the sigmoidovaginostomy supported the sigmoidovesicostomy. There was also one instance of ileus, necessitating gastric suction for 5 days.

Follow-up examinations have been possible on all patients. All but one have a vagina that requires instrumentation to reach the apex of the vault. The line of the anastomosis is clearly demonstrable in the change from the atrophic, pale, smooth vaginal mucosa to the pink, redundant mucous membrane of the bowel. The discharge of mucus from the bowel, though relatively small in amount, is such that most of these patients have preferred to use douches occasionally, and all patients have been advised to wash out the bit of inspissated mucus that sometimes forms and remains at the apex of the segment of bowel.

Intercourse has been completely normal for both partners for 4 patients. In one patient, who has an atrophic and small introitus, lubricants are necessary, and in another, intercourse is reported as fair-togood and improving. One reports adequate room but some discomfort, requiring lubricants.

In all the patients reported herein, the operation was indicated primarily for com-

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plications resulting from the treatment of a serious disease; the reconstruction of the vagina was a secondary consideration. However, from the experience obtained in these cases, it seems justifiable to advise exploration for possible sigmoidovaginostomy when the primary lesion appears to be controlled and the patient believes that additional vaginal depth would be of real benefit to her.

Summary

A new method has been described for anastomosing a short segment of sigmoid to the vaginal vault by an oblique end-to-end anastomosis for the purpose of gaining added length and lubrication of the vaginal canal. This method is particularly applicable patients with loss of vaginal depth after treatment of genital malignant lesions, who in addition have complications such is fistula, ulceration, stricture, or recurrence of the malignant lesion—disorders that require transection of bowel. The cases of 7 patients in whom such an operation was performed with no postoperative complication from the additional operative procedure have been presented. The postoperative vaginal depth has ranged from average to excessive. The additional depth has relieved dyspareunia, and 5 of 7 patients report intercourse to be satisfactory and normal without the use of lubricants.

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Discussion

Dr. Bayard Carter, Durham,-North Carolina. I wish I might bring some experience to the discussion of Dr. Pratt's paper. Unfortunately, we have not performed this operation either after the extended operation for cancer of the cervix or endometrium or on patients in whom exenterative operations have been done.

We have always made it a policy, after the extended operation for cancer of the cervix or cancer of the endometrium, to have the patients use a vaginal mold to lengthen the depth of the lower one third of the vagina which is left at operation. In many there have been good results; in many irradiated patients the results are poor.

In our patients upon whom total exenterative operations have been done we have had a few

successes by creating, by incision, a perineal tract and by the use of various sized obturators to deepen the tract as epithelium grows into it.

DR. CLYDE L. RANDALL, Buffalo, New York. I would like to ask Dr. Pratt if the Baldwin operation, utilizing a loop of small bowel from which considerable mucus is discharged, would not create a greater problem than should be expected when a loop of sigmoid is employed.

DR. PRATT (Closing). Dr. Randall has brought up the question of the amount of mucus from the segments of sigmoid. Baldwin's original the ught was to use the sigmoid, but since it was not suitable in the case he had planned to utilize in the

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small bowel was used instead. Baldwin's name has been connected with the small bowel ever since. The disadvantage of the use of the ileum is the excessive, irritating mucus that is sometimes produced, while with the sigmoid there is only a slight amount of mucus and yet there is enough for lubrication. Actually some of the mucus inspissates and forms plugs 1 cm. or so

in diameter and that is why the patients prefer to use douches once or twice a week. Also the sigmoid is a thicker organ and does not traumatize so easily as the small bowel and it does not bleed so easily. When the small bowel is used, pain around the umbilicus following intercourse is sometimes complained of, whereas with the sigmoid that is not true.

Chorioadenoma destruens

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IN THE files of the Mayo Clinic we have records of 20 cases of chorioadenoma destruens, or invasive mole. During the search for these cases we noted 87 molar pregnancies and 17 choriocarcinomas. Of the 3 common trophoblastic lesions-hydatidiform mole, choriocarcinoma, and chorioadenoma destruens—the last-mentioned entity is probably of the most importance. This statement is made in light of the observation that this trophoblastic lesion is frequently diagnosed incorrectly as a choriocarcinoma and thereby given a most unfavorable prognosis. The inaccuracy in diagnosis is not necessarily due to improper interpretation of tissue by the pathologist but is more often due to clinical findings of metastatic lesions. Thus, the clinician, faced with a history of a molar pregnancy, the persistent presence of chorionic gonadotropin in the urine, and evidence of metastasis is often certain that he is dealing with a choriocarcinoma which is, for the most part, eventually fatal. In 8 of our 20 cases of chorioadenoma destruens there was roentgenographic evidence of pulmonary involvement. This finding alone, on occasion, led us to err in the evaluation of the prognosis of certain patients. It was pri-

marily because of this high incidence of presumed involvement of the lung that we decided to present this series of cases. th

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Chorioadenoma destruens as a metastasizing lesion

In 1947, Hertig and Sheldon¹ wrote that an invasive mole rarely if ever metastasizes—this after a review of 32 cases. In 1956, Hertig and Mansell² wrote that in spite of the usually benign outcome, clinically evident metastasis may occur. Novak and Seah,3 in reviewing the cases recorded in the Mathieu Memorial Chorionepithelioma Registry, wrote in 1954 that in spite of the local invasiveness of such moles there is little tendency to distant metastasis. These authors reported, however, that exceptions did occur and noted 6 such instances of metastasis. Greene,4 in updating the registry material in 1959, wrote that of 42 cases of chorioadenoma destruens definite metastasis had been noted in one site or another in 11 cases, with metastatic lesions being present in the lungs in at least 6.

There has been speculation that roentgen evidence of metastatic disease may be erroneous, as the shadows seen may be due to the reaction of some totally unrelated condition such as a granuloma or even atypical bronchopneumonia rather than due to invasion of the parenchyma of the lung by trophoblastic tissue. This seems unlikely in view of the increasing number of pulmonary metastatic lesions proved by biopsy of pulmonary tissue. Among the reported cases in which this procedure has been done are

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The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Presented at the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960.

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those of Delfs,⁵ Reed and co-workers,⁶ and Jacobson and Enzer.⁷ The case (Case 16 in our series) of Jacobson and Enzer is included in this report, as the patient was at one time a patient at the Mayo Clinic. We have confirmed the presence of a metastatic lesion by biopsy of the lung in another of this series (Case 18). There can be little doubt, therefore, that this entity does result in metastasis to the lungs and that positive roentgen findings are likely to represent metastatic disease.

Pathologic considerations

Since Schmauch,8 in 1907, referred to this entity as a destructive mole and Ewing,9 in 1910, gave it the name of chorioadenoma destruens, much has been written about its pathologic features. Presently there seems to be general agreement that chorioadenoma destruens presents a microscopic picture of considerable trophoblastic hyperplasia always associated with villus formation. There is anatomic evidence of invasion into the myometrium and not infrequently extension beyond the confines of the uterus. Novak,3 in one of his last communications on the subject, held that the diagnosis of choriocarcinoma was unlikely if one or more villi were found, but stated that, occasionally at least, a villus could be present in a chorionepithelioma. We agree with Greene⁴ in defining chorioadenoma destruens as a lesion in which there has been invasion by the mole into or through the uterine wall or metastasis, or both, and which contains one or more well-formed villi. In this report we have included all our cases that have met this definition.

Clinical features

Chorioadenoma destruens, or invasive mole, by definition should always follow a molar pregnancy. Among the patients who have experienced such a pregnancy, those in whom chorioadenoma destruens develops usually have persistent vaginal bleeding which may vary from intermittent spotting to exsanguinating hemorrhage, pelvic findings suggestive of a pathologic process, and persistent urinary excretion of chorionic gonadotropin. The salient features of our 20 cases are presented in Table I. All 20 patients survived.

It is important to note that in a number of our cases much or all of the therapy was carried out in the patient's home community and that often we saw patients only for recommendation as to proper treatment. Not uncommonly the condition had been diagnosed as choriocarcinoma and the patient had therefore been given a hopeless

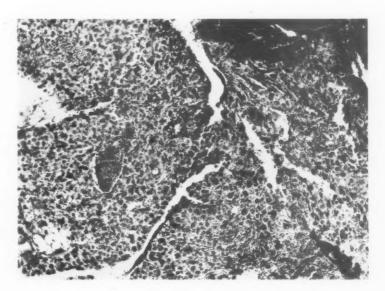


Fig. 1. Case 7, solid masses of amplastic trophoblast from one of several hemorrhagic nodules buried deep in the uterine wall. In the absence of villi the diagnosis of choriocarcinoma seemed justified. (Hematoxylin and eosin. ×55.)

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Table I. Summary of cases

Case	Age and date admitted	Gravid-	Parity	Weeks of molar preg- nancy	Luetein- ization including cysts	Chorionic gonadotropin level before treatment	Treatment	gonad
1	20 (July, 1939)	1	0	8	Positive	1,000 R.U.† 66 R.U.‡	Hysterectomy, oophorectimy, x-ray of chest, pelvis	1,000 R ative
2	36 (July, 1945)	1	0	18	Negative	5,000-10,000 R.U.†	Curettage 3 times, hysterectomy, left oophorectomy	Not dete
3	25 (February, 1946)	3	2	15	Negative	Pregnancy tests only, positive	Curettage, x-ray of pelvis, chest, hysterectomy, oophorectomy	Negative treatm
4	36 (December, 1947)	3	2	15	Positive	250,000 R.U.† 275,000 R.U.‡	Curettage, hysterectomy	Positive (
5	24 (September, 1947)	2	0	15	Positive	720 I.U.	Curettage, hysterectomy, oophorectomy, x-ray of pelvis	Negative
6	23 (January, 1949)	2	1	13	Positive	56,500 I.U.	Curettage, hysterectomy, oophorectomy, x-ray of chest, pelvis	Negative 4 years
7	20 (July, 1949)	1	0	15	Positive	37,491 I.U.	Curettage, hysterectomy, oophorectomy, x-ray of pelvis, chest	Negative
8	30 (September, 1949)	2	1	10	Negative	42,378 I.U. (see case report)	Curettage, exploration, x-ray of chest, pelvis, local excision of vaginal nodule	Became no ing the
9	45 (August, 1950)	8	6	12	Positive	7,952 I.U.	Curettage, hysterectomy, oophorectomy	Negative
10	21 (January, 1950)	3	2	17	?	19,096 I.U.	Curettage 3 times, excision of vaginal nodule, radium, x-ray	Negative
11	24 (June, 1951)	1	0	13	?	"Positive" at home	Curettage, hysterectomy	Negative (
12	26 (September, 1951)	2	1	17	Negative	11,070 I.U.	Curettage, 3 times, hysterectomy oophorectomy	393 I.U I.U. (3) (4)
13	26 (July, 1953)	1	. 0	7	Negative	16,200 I.U.	Hysterotomy, curettage, hysterectomy	regnance negative
14	33 (June, 1954)	7	4	11	Negative	Pregnancy test positive	Primary hysterectomy for mol (at home)	
15	35 (August, 1954)	2	1	7	Negative	23,751 I.U.	Curettage, hysterector	

	(horionic gonadotropin level*	Chest roentgenogram	Patient alive and well, years (to 1960)	Remarks
у,	1,000 R.U. (11), neg- ative (19)	Negative	20	Invasive mole involving myometrium, 5 cm. nodule, left cornu; referral diagnosis, choriocarcinoma
ctomy,	Not determined	Negative	15	7 mo. from passage of mole to hysterectomy; intermit- tent bleeding and chorionic gonadotropin present dur- ing this time with negative curettages; at hysterec- tomy, molar tissue invading myometrium
chest, my	Negative during x-ray treatment to pelvis	Positive	14	Considered choriocarcinoma because of multiple small densities in chest roentgenograms; pregnancy tests negative during treatment of pelvis and before treatment of chest and hysterectomy; villi noted in myometrium
	Positive excess amount (1); negative (10)	Positive	13 ,	7 wk. after delivery of mole at home; transfusions at home; severe hemorrhage after admission; invasive mole noted in hysterectomy specimen
pelvis	Negative (1)	Negative	13	Original diagnosis, choriocarcinoma, infiltrating lesion 2 by 2 cm.; revised diagnosis, chorioadenoma destruens
chest,	Negative (4) and for 4 years	Positive	11	Original diagnosis, choriocarcinoma; curettage negative prior to hysterectomy; persistent but not alarming bleeding; vaginal metastasis, penetration into left broad ligament
pelvis,	Negative (1)	Negative	11	See case report
-ray of sion of	Became negative dur- ing therapy	Positive	11	See case report
	Negative (1)	Negative	4	Curettage negative; invasive mole 3 cm. in diameter to within 3 mm. of peritoneum and extension for 6 cm. in vein of right broad ligament
n of n, x-ray	Negative (3)	Negative	10	Much hemorrhage from vaginal lesion; this with sepsis prevented operation; chorionic gonadotropin negative 3 wk. after completion of therapy; vaginal nodule, invasive mole
	Negative (6)	Negative	9	Perforation through uterus with intra-abdominal hemor- rhage; many chest symptoms but chest x-ray broncho- scope examination, etc., negative
rectomy	393 I.U (2); 1,953 I.U. (3); negative (4)	Positive	9	Myometrial penetration with intravascular extension; no x-ray treatment as chorionic gonadotropin decreasing and chest lesions steadily regressed
	regnancy tests only, negative (4)	Negative	7	All definitive treatment at home; seen by us because of persistent bleeding after hysterotomy with persistent chorionic gonadotropin titer; hysterectomy advised; mole invaded myometrium
for mol	,	Positive	4 (to 1958)	Myometrial invasion; vagina wall metastasis, positive for destruens; positive chest; titer became negative with no further treatment; patient followed closely, had un- eventful recovery
	1	Negative *	6	Much hemorrhage, sepsis; large penetrating lesion right horn of uterus to within 5 mm. of peritoneum

Table I-Cont'd

Case	Age and date admitted	Gravid- ity	Parity	Weeks of molar preg- nancy	Luetein- ization including cysts	Chorionic gonadotropin level before treatment	Treatment
16	22 (August, 1955)	1	0	12	Positive	Pregnancy tests only, positive in dilution 1:800	Hysterotomy, curettage
17	43 (September, 1955)	2	0	12	Positive	Not done	Curettage, hysterectomy, oophorectomy
18	36 (December, 1955)	12	10	9		84,000 R.U. (elsewhere)	Curettage, hysterectomy, x-ray of chest, pelvis; radium
19	20 (January, 1956)	1	0	12		29,700 I.U.	Curettages, hysterectomy, radi- um, x-ray
20	19 (June, 1960)	1	0	14	Positive	1,497 I.U.	Curettage, local excision

*Weeks after treatment in parentheses.

†Prolan A.

Prolan B.

prognosis (Cases 1, 3, 8, 11, and 17). We, too, made this error in diagnosis, particularly in Cases 6 and 7.

Unfortunately, the assay data in most of our cases do not permit a statement as to how quickly chorionic gonadotropin disappears from the urine after removal of the persistent molar tissue. In those patients in whom relatively frequent assays were done, chorionic gonadotropin disappeared from the urine within 1 to 4 weeks. Cases 5, 6, 7, 9, and 12 are examples of this rapid disappearance. There can be little doubt that close observation of the excretion of chorionic gonadotropin is of paramount importance in the determination of the type of therapy and its efficacy.

Pulmonary lesions. In 8 of our 20 cases there was roentgenographic evidence of metastatic pulmonary involvement. In Cases 16 and 18, proof of such involvement was obtained by biopsy of pulmonary tissue. We agree with Reed and associates and Jacobson and Enzer that such an examination is extremely worth while for diagnostic and prognostic purposes. It would seem likely

that in the future all patients such as these, unless there is an unequivocal diagnosis of choriocarcinoma, may and should have biopsy of pulmonary tissue, as the necessary thoracotomy is practically devoid of risk.

The cases in which there was pulmonary involvement are listed in Table II. One lung was involved in 4 instances and both lungs in the remaining 4.

In all instances the roentgenographic evidence of pulmonary involvement disappeared. The time required for it to disappear varied considerably. In patients who had x-ray examination of the thorax at satisfactorily frequent intervals the longest time required for complete resolution was 8 months.

Evidence of chorionic gonadotropin excretion was associated with roentgen evidence of metastatic disease of the lung in 7 of the cases (Cases 3, 4, 6, 8, 12, 16, and 18). In 4 cases (Cases 3, 4, 6, and 16), after definitive treatment of the primary lesion, the assay for chorionic gonadotropin became negative prior to disappearance of the roentgen evidence of the disease. In 3 cases

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Cases

Chorionic gonadotropin level*	Chest roentgenogram	Patient alive and well, years (to 1960)	Remarks
Pregnancy tests posi- tive in decreasing di- lutions; chorionic gonadotropin nega- tive (12)	Positive	5	No myometrial invasion; chest lesions after hysterotomy; positive lung biopsy with negative chorionic gonadotropin titer; see report of Jacobson and Enzer
Negative (20)	Negative	5	Choriocarcinoma diagnosed at home; patient seen by us, negative examination; tissue review with diagnosis of destruens; deep myometrial invasion
4,883 I.U. (4); 1,551 I.U. (8); 892 I.U. (10); negative (14)	Positive	5	See case report
10,738 I.U. (3); 1,265 I.U. (5); negative (13)	Negative	4	Very severe hemorrhage; invasion into broad ligaments extensive; operation hemorrhage so marked doubtful all tissue removed; extensive radiation therapy given
Negative (1); negative (6)	Negative	3 mo.	See case report

(Cases 12, 14, and 18) the assay evidence indicated that the probable trophoblastic lesions continued to function after the primary lesion had been removed. In one case (Case 8) the disease process in the pelvis was so extensive that only intensive roentgen therapy was administered to the pelvis and lungs. The details of this case are given subsequently. In Cases 12, 14, and 16, after primary treatment to the pelvis, no additional therapy was administered, as excretion of chorionic gonadotropin either decreased or was lacking. In all instances these patients recovered and the pulmonary lesions disappeared.

Detailed reports of Cases 7, 8, 18, and 20 follow.

Report of cases

Case 7. A 20-year-old white woman, gravida i, para 0, was examined on July 25, 1949, and found to have a blood pressure of 170 mm. Hg systolic and 85 diastolic which was associated with Grade 2 albuminuria and a hemoglobin value of 7.0 Gm. per 100 c.c. The last menstrual period had started on April 23, and intermittent vaginal bleeding occurred for 2

weeks. On July 29 a roentgenogram of the abdomen revealed a small calcified fetus in a large uterus. A diagnosis of a combined normal and molar pregnancy was made. On August 1 the chorionic gonadotropin excreted in the urine totaled 37,491 I.U. in 24 hours.

On August 4 the patient expelled a dead 3 month fetus along with considerable molar tissue. One thousand cubic centimeters of blood was given. Dilatation and curettage was done

Table II. Patients with pulmonary involvement

	Involvement	
Pa- tient	Extent	Time to clear, weeks
3	Multiple, both lungs	7 -1-2
4	Left lower lobe	6
6	Left upper lobe	22
8	Right fourth interspace	See case report
12	Throughout both lungs	7
14	Both lobes, left lung	*
16†	Left upper lobe, left mid- lung field	37
18	Multiple, both lungs	24

^{*}Lungs cleared; time required not known. †Case reported by Jacobson and Enzer.⁷



Fig. 2. Case 7, prolonged search in a review of the material from this case revealed occasional villi such as the one depicted here. The diagnosis was correctly revised to chorioadenoma destruens. (Hematoxylin and cosin. ×55.)

on August 7 and August 11. There was no further bleeding. The value for chorionic gonadotropin on August 13 was 2,427 I.U. On September 5, spotting was noted and the value for chorionic gonadotropin had increased to 6,334 I.U. On September 19, profuse bleeding occurred with the passage of some hydatid vesicles. The value for chorionic gonadotropin was now 6,083 I.U. The x-ray appearance of the chest was negative and the value for hemoglobin was 11.7 Gm.

Another dilatation and curettage, done on September 22, 1949, was followed by total abdominal hysterectomy and bilateral salpingooophorectomy. The tentative pathologic diagnosis was chorionepithelioma (Fig. 1). On September 28 the value for chorionic gonadotropin was zero. Deep x-ray therapy was given to the pelvis and chest from October 4 to October 10. The patient did well without further difficulty. The results of follow-up examinations in 1952 and 1955 were normal. In June, 1960, the patient wrote that she was well.

Comment. The tissue removed at the time of hysterectomy was reviewed and the correct diagnosis was established (Fig. 2).

This case was mentioned by Hunter and Dockerty¹⁰ in their report on choriocarcinoma. We have included it here because

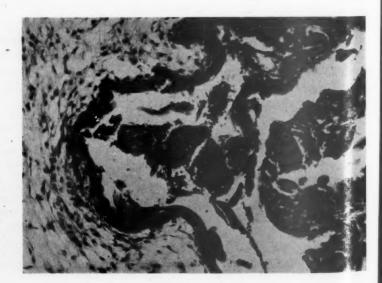


Fig. 3. Case 18, material from the hysterectomy specimen. Although islands of anaplastic trophoblast are present, the coexistence of an edematous villus certifies the diagnosis of penetrating mole. (Hematoxylin and eosin. ×150.)

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the importance of persistent excretion of chorionic gonadotropin is so well illustrated, as is the ease with which choriocarcinoma can be mistakenly diagnosed. If the tissue illustrated in Fig. 1 had been the only tissue submitted (and nearly all the sections were similar to this section) to the pathologist or to a registry for examination, the case would have undoubtedly been accepted as one of choriocarcinoma with cure. However, diligent search revealed the microscopic picture shown in Fig. 2, and the correct diagnosis was made.

Case 8. A 30-year-old white woman, gravida ii, para i, had had for 10 weeks prior to admission a molar pregnancy that had been terminated by dilatation and curettage on May 25, 1949. The diagnosis was hydatid mole without undue hyperplasia or anaplasia. In August the referring physician noted an enlarged uterus and a large right adnexal mass and explored the pelvis. A perforating neoplasm was encountered, with involvement of the retroperitoneum. A specimen for biopsy was obtained. The pathologist who examined the tissue made a diagnosis of choriocarcinoma on the basis of trophoblastic anaplasia in a picture very different from that observed in the original mole.

The patient was admitted to the Mayo Clinic on Sept. 19, 1949, at which time the uterus was two to three times normal size. She had a large right pelvic tumor. Also noted was a firm red nodule in the anterior portion of the vagina approximately 2 cm. in diameter. X-ray examination of the chest revealed a nodular metastatic lesion at the level of the right fourth intercostal space, and the value for chorionic gonadotropin was 42,378 I.U. in 24 hours. Tissue sent by the referring physician was diagnosed by us as showing chorioadenoma destruens. The vaginal nodule was excised. Although microscopic examination disclosed only necrotic tissue and blood clot, it was thought reasonably certain that the former was necrotic trophoblast and that the lesion was a metastatic one. The major treament elected was deep x-ray therapy to the pelvis and lungs.

Three courses of such therapy were administered between Sept. 26, 1949, and Feb. 7, 1950. With this therapy the chest lesion disappeared by Jan. 17, 1950, although the value for chorionic gonadotropin on this date was 1,148 I.U.



Fig. 4. Case 18, reproduction of roentgenogram showing scattered nodules in both lung fields. The appearance is that of a metastatic malignant process.

X-ray examination of the chest and assay for chorionic gonadotropin gave negative results on Feb. 6, 1950. During this time the very marked pathologic changes in the pelvis regressed until only postirradiation induration and thickening were evident.

The patient was seen for physical examination, x-ray examination of the chest, and assay of chorionic gonadotropin at intervals of 6 to 12 months until March 24, 1954. The results of all the follow-up examinations were negative and the patient wrote on June 24, 1960, that she had had no further difficulty.

Comment. This case is of particular interest because of the complete response to radiation therapy. At the time of admission the extent of the pelvic disease precluded surgical removal. Even though the pathologic diagnosis was chorioadenoma destruens, the marked increase of chorionic gonadotropin, the metastatic lesion in the lung, and the extensive pathologic changes in the pelvis made a clinical diagnosis of choriocarcinoma seem most likely. The clearing of the chest in 4 months, the disappearance of the chorionic gonadotropin from the urine in 41/2 months, and the continued wellbeing of the patient confirmed the pathologic designation of chorioadenoma destru-

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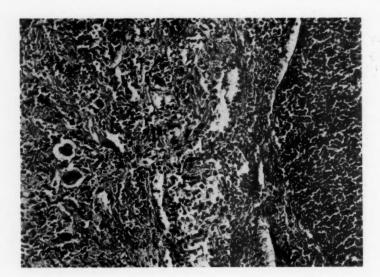


Fig. 5. Case 18, section from a pulmonary nodule showing isolated trophoblastic cells enmeshed in a hemorrhagic matrix along with an intense inflammatory component. (Hematoxylin and eosin. ×150.)

Case 18. A 36-year-old white woman, gravida xii, para x, had her last menstrual period beginning on July 12, 1955. On September 14, dilatation and curettage was done with removal of a hydarid mole. On October 12, hemorrhage occurred, transfusions were given, and dilatation and curettage was done a second time with the removal of more molar tissue. On October 26 the value for chorionic gonadotropin was 58,000 R.U. and on November 14 it was 84,000 R.U. Severe exsanguinating hemorrhage occurred on November 21 and necessitated emergency total abdominal hysterectomy on this date. The diagnosis made by the home pathologist was chorioadenoma destruens (Fig. 3).

On Dec. 2, 1955, x-ray examination of the

chest showed multiple metastatic lesions, and on December 17 the value for chorionic gonadotropin was 83,000 R.U. In spite of the pathologic diagnosis the home physician felt that the patient must have a choriocarcinoma and he referred the patient to us on December 16.

X-ray examination revealed multiple metastatic lesions in both pulmonary fields (Fig. 4). Our first assay of chorionic gonadotropin, on December 19, showed a value of 4,883 I.U. Thoracotomy was done on December 20, and biopsy of pulmonary tissue showed a typical picture of metastatic trophoblast (Fig. 5). Our fresh frozen sections showed well-formed villibut, regrettably, we have no fixed sections which show these structures. From Dec. 28, 1955, to

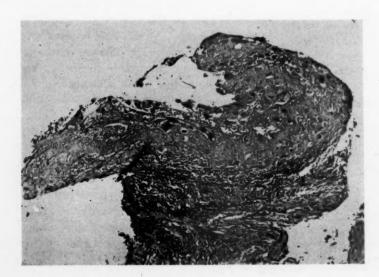


Fig. 6. Case 20, the hemorrhagic, deeply penetrating nodule, locally removed from the uterus in this case, displayed scattered villi with degeneration and hyalinization of trophoblast. Such alterations, as here depicted, sometimes correlate with low or dropping values of chorionic gonadotropin. (Hematoxylin and eosin. ×75.)

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Jan. 7, 1956, 1,400 mg. hr. of radium was administered to the vaginal vault, and concurrently the pelvis and thorax were subjected to deep x-ray therapy.

The values for chorionic gonadotropin were as follows: Jan. 3, 1956, 3,140 I.U.; January 7, 3,477 I.U.; January 23, 1,551 I.U.; February 9, 892 I.U.; and March 10 and thereafter to Aug. 26, 1958, none. By June 25, 1956, the x-ray appearance of the chest had cleared. In a letter received on July 12, 1960, the patient stated that she was well except for some discomfort occasioned by a recent operation on the gall-bladder.

Comment. This case would seem to illustrate almost all of the important diagnostic and treatment problems that could be associated with chorioadenoma destruens: difficulty in diagnosis; severe and repeated hemorrhage; successful accomplishment by the home physician of a difficult surgical procedure in a patient who was critically ill because of acute blood loss; persistent and prolonged excretion of chorionic gonadotropin after a definitive pelvic operation; metastasis to the lungs; correct diagnosis by biopsy of pulmonary tissue; treatment with radium and x-rays; and eventual cure.

The specimen of lung removed for biopsy, like that reported by Jacobson and Enzer, contained chorionic villi, which clearly established the diagnosis of chorioadenoma destruens.

Case 20. A 19-year-old white woman, gravida i, para 0, had her last menstrual period beginning on Jan. 18, 1960. On April 26, 1960, dilatation and curettage was done, with removal of the products of a molar pregnancy. Vaginal bleeding continued and a pregnancy test gave positive results in a dilution of 1:800. Minimal and intermittent vaginal bleeding persisted and the pregnancy test still gave positive results on May 31. The patient was then referred to the Mayo Clinic.

The patient was first examined by us on June 3, 1960. A dirty reddish vaginal discharge was present and enormous bilateral compound lutein cysts were noted. On June 9 the value for chorionic gonadotropin was 1,497 I.U. X-ray examination of the chest gave negative results.

On June 10, 1960, Dr. R. E. Symmonds, of our section of obstetrics and gynecology, did a dilatation and curettage and obtained no tissue. This was followed immediately by abdominal exploration. Both ovaries were excessively enlarged by lutein cysts which required evacuation before the uterus could be elevated. Through a hysterotomy incision a single nodule 1.5 cm. in diameter was palpated deep in the miduterine wall and was removed (Fig. 6).

On the second postoperative day the patient's breasts became engorged, and on the ninth postoperative day examination revealed a normal pelvis. On June 18, 8 days postoperatively, there was no chorionic gonadotropin in the urine. On July 18 and August 18 the test for this substance again gave negative results as did the pelvic examinations. Chest x-ray examination on August 18 gave negative results.

Comment. This is a rather typical case of chorioadenoma destruens. The patient had continued bleeding, persistent excretion of chorionic gonadotropin, and enormous lutein cysts. The unusual feature was the conservative treatment employed. As but a single nodule could be palpated deep in the uterine wall, it alone was removed. The immediate frozen-section diagnosis of chorioadenoma destruens permitted this procedure. The possibility that invasive molar tissue might remain in the uterine wall was entertained. However, the chance of maintaining the reproductive function in this young woman made this conservative procedure seem worth while. Furthermore, if such tissue had been left, chorionic gonadotropin would have continued to be present and a second operation with hysterectomy or other therapy could have been employed.

To our knowledge such a conservative procedure for the correction of chorioadenoma destruens has not been previously attempted. It is too soon to know whether or not this treatment was in the best interests of the patient but we believe that it will ultimately prove to have been so.

Comment

Review of our 20 cases of chorioadenoma destruens, or invasive mole, has shown the not infrequent difficulty in establishing the correct diagnosis. This difficulty occurred in some cases because of the scarcity of well-formed villi in most of the pathologic material. In many cases, without the firm establishment of the correct diagnosis, the clinical findings of bleeding, persistent excretion of chorionic gonadotropin, and evidence of metastasis led to a strongly presumptive diagnosis of choriocarcinoma.

Although not germane to this report we note here that our examination of molar tissue did not enable us to predict, from the microscopic picture, those moles that would or would not invade, or become choriocarcinomas.

Confirmed was the observation of others that the microscopic anaplasia seen in the penetrating or "metastasizing" trophoblast was not always the same as that found in the original mole. In nearly all instances in which material from both sources was available for study, the "destruens" part of the picture was more worrisome than was its earlier evacuated counterpart.

Along this same line it was noted that necrosis of muscle and areas of hemorrhage could be fully as prominent in destruens lesions as in the lesions of true choriocarcinoma that we had in our collection. In fact, several of our cases from this series had been catalogued as choriocarcinoma until repeated studies of the formalin-preserved specimens revealed the presence of true villi. Pronounced degenerative changes in the trophoblast along with hyalinization of both stromal and epithelial elements were interesting features which correlated with low or dropping levels of chorionic gonadotropin. In only one of our cases could these alterations be attributable to a possible roentgen-ray effect. Undoubtedly the processes represent a retrogressive chain of events of uncertain etiology which highlight the difference between the uncontrollable growth of cells in choriocarcinoma on the one hand and the disappearance of the secondary deposits of chorioadenoma destruens on the other.

Two other features were of interest. One concerned the presence in three removed

uteri of adenomyomatous nodules at the site of molar penetration. In one of these cases the endometrial stromal cells within the adenomyoma had undergone extensive decidual alteration. Pessin¹¹ has observed this phenomenon and wondered about the possible role of adenomyomas in inducing penetration of the uterine wall by molar tissue. The second feature concerned the occurrence of a decidual reaction involving the peritoneum of the cul-de-sac in 2 of our patients. No endometrium-like glands were present in these lesions. The presence in one of these patients of an associated tarry cyst of one ovary lends support to the notion that the decidual reaction was perhaps an example of endometriosis and that glands would have been encountered if sufficient material had been available for study.

There was roentgen evidence of pulmonary involvement in 8 of the 20 cases, vaginal metastasis in 2, and retroperitoneal extension in 2. These findings, in most instances in the past, have led to giving the patient a hopeless prognosis. This report shows that such a prognosis is not indicated until thorough examination of tissue from the pelvis and, if need be, from the lung or other metastatic site shows the absence of villi in the trophoblastic tissue in all locations. We believe, quite strongly, that the presence of villi in invasive or metastasizing trophoblastic tissue excludes the diagnosis of choriocarcinoma and indicates the need for intensive treatment with all available modalities. We have had no reason to employ amethopterin in any of our patients; however, this or other antimetabolites might be useful in certain cases.

The persistent excretion of chorionic gonadotropin in the urine in elevated amounts in any patient with this disease is, to us, evidence of active disease. Whether or not x-ray therapy or biopsy of the lung or other metastatic lesions is necessary with negative or falling excretion of chorionic gonadotropin is debatable. One can take the view that, with such evidence, the process is resolving and nothing will be gained by x-ray therapy or biopsy. This cannot be

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denied, as is shown by a number of our cases. The opposite argument is that by biopsy the diagnosis is established, disease, other than chorioadenoma destruens, is ex-

cluded, the patient has peace of mind and, by means of x-ray therapy, the resolution of the disease process will be made more certain.

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Discussion

Dr. John B. Montgomery, Philadelphia, Pennsylvania. Twenty cases of chorioadenoma destruens or invasive mole constitute an unusual experience in one institution. The most striking feature of Dr. Wilson's report is the high incidence of lung metastases (8 in 20 cases) with no deaths. This contrasts sharply with the 42 cases reported by R. R. Greene from the Mathieu Registry among which there were 11 metastatic lesions and 6 deaths. Three of the deaths occurred in patients with pulmonary lesions, although 3 others who had lung lesions survived. Histologic confirmation of chorioadenoma destruens in the lung was made in only one of Greene's cases. On the other hand, the 32 cases reported by Hertig with no metastases and no deaths, except one from sepsis, supports the relatively benign nature of this lesion.

The x-ray diagnosis of lung metastases in the 8 patients was supported by biopsy in 2 instances. It is noted that similar confirmation has been reported by at least 3 other authors. Although the x-ray diagnoses are very likely correct, we agree with Dr. Wilson that in the future such diagnoses should be confirmed by lung biopsy whenever such a procedure seems reasonable.

The survival of all of Dr. Wilson's patients seems to indicate clearly that the accepted practice of prompt removal of the primary lesion plus the use of x-ray therapy in appropriate cases may be regarded as effective treatment. A review of the protocols, however, reveals several interesting variations in this plan, probably because many of the patients were pri-

marily treated elsewhere. Hysterectomy was done in 17 patients, and the ovaries were conserved in 7 of them. In one patient the diagnosis was made only by lung biopsy after the removal of a benign mole by hysterotomy. No further treatment was given. Two other patients with lung lesions required no x-ray therapy.

The most interesting variation in therapy occurred in Case 20 in which at laparotomy the operator had the courage to excise a local lesion in the uterine wall and conserve the uterus after a frozen section revealed an invasive mole. Only 4 months have elapsed but the hormone levels remain normal and the patient appears to be well.

Perhaps this interesting case may point the way to more conservative management of some patients. It was unfortunate that one half of Dr. Wilson's patients were without children. In all but this one case it was necessary to remove the uterus and, in some instances, also the ovaries.

The diagnosis of this disturbing lesion can be made rarely from uterine curettings. Abdominal exploration and removal of the uterus to provide adequate tissue for diagnosis has been the procedure of choice. Removal of the primary lesion has been regarded as important or possibly essential to cure. Perhaps we are justified now in questioning this attitude. When endometrial curettage reveals no tissue and the chorionic gonadotropin assay remains elevated, early abdominal exploration and local excision of tissue for biopsy may be justifiable.

In such cases, perhaps the use of folic acid antagonists and careful observation of the hormone titer as suggested by Gordon W. Douglas and others may result in more frequent conservation of the childbearing function.

DR. ARTHUR T. HERTIG, Boston, Massachusetts. Dr. Wilson's paper illustrates several important features, the most important one being that chorioadenoma destruens is not always the most easily diagnosed of the trophoblastic complications of mole. Hence, we might comment a little on what some of the difficulties in making a correct diagnosis are.

The correct diagnosis is made usually from an intact uterus or a significant portion of the uterine wall, such as in Case 20, with enough sections-and this is important-to rule in the presence of hydropic villi. This criterion is necessary because James Ewing created this definition of an invasive mole or chorioadenoma destruens and said that it had invasive villi. Since these hydropic villi are usually small (and I have never found, in the 50 or 60 of these cases that I have seen, a large hydropic villus), they are always of the order of 2 or 3 or possibly 4 mm. in diameter. Since these villi are small or medium in size, the blocks from which the diagnosis is made—and they should be serial blocks-must necessarily not be more than 2 or 3 mm. thick and, therefore, a random section must be taken somewhere from this block. Otherwise, there is a great danger of making a diagnosis of choriocarcinoma simply because the peripheral portion of the invasive mass of trophoblasts attached to the molar villus is able to invade. By its very nature it is anaplastic and does not necessarily resemble choriocarcinoma, but it may and hence the diagnosis of the latter condition may be erroneously made. Serial blocks, therefore, are necessary for the diagnosis to be made. Seldom can chorioadenoma destruens be diagnosed from curettage of the uterus. I have done it on occasion, or at least I suspected it because of contiguity of myometrium with anaplastic trophoblast arising from a villus.

The second point that this superb paper brings out is the increasing evidence that these usually benign lesions of chorioadenoma destruens do on occasion have metastatic lesions. I have seen a number of these in the past 15 years. It has been commented that in the 32 cases that Sheldon and I reported none of the patients showed metastases. I might point out that in that series

of 200 moles, of which there were 32 choricadenoma destruens, the moles were contributed from all over the country mainly for morphelogic evaluation of the mole. Hence, follow-up was not necessary or may not necessarily have been as complete as in the Mayo Clinic group or in the registry cases. Therefore, the fact that these 32 cases are listed in the literature as not having any sequelae other than one death from sepsis may or may not be strictly accurate in terms of follow-up facts. We are now accumulating very good evidence roentgenographically and by biopsy that these trophoblastic villous lesions in the uterus do break off, by some mechanism not yet understood, and migrate by the vascular system to the lungs. This migration to the lungs occurred in 8 out of 20 cases, to the vagina in 4 cases out of 20, and to the retroperitoneal region in 2 cases out of 20. We have seen examples of all of these in the course of time so we are in hearty agreement with these superb observations of Dr. Wilson and his group.

I would like to raise the question as to whether one must necessarily have a deported villus to either the vagina, lung, or retroperitoneal region from a true invasive mole to have a bona fide diagnosis of metastasis in this condition. I think that there may be a deported villus. I have seen histologic evidence of it and also histologic evidence without the villus.

The third point that has been brought out in this paper is the treatment by x-ray in 9 out of the 20 patients, with apparent acceptance of it as a reason for the cures in some instances. I think about the built-in mechanism of involution which the trophoblast has, whether it is normal or neoplastic in the uterus or normal or neoplastic but deported to the lungs. In any case the Lord built into the trophoblast its fundamental spontaneous mechanism of involution, the details of and the reason for which we know absolutely nothing about. I would query whether, in spite of the fact that 9 out of the 20 patients had x-ray treatment, there is any real evidence that trophoblast of this general degree of differentiation is a radiosensitive tissue. I personally do not think so but an opinion is a long way from fact.

As to the treatment, the fourth main part of this fine paper, the local excision cited in Case 20 is most interesting. I think the authors are quite correct in that this is the first published instance of successful treatment by this method. We have, however, recommended it on occasion

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art of Case rs are lished ethod. casion to our consultation contributors for their patients who have had a mole with some or all the clinical or hormonal sequelae of subinvolution of the uterus, bleeding in spite of repeated curettage, rising titer, or other evidence of persistence of trophoblast of unknown nature. Statistics show a patient with hydatidiform mole and sequelae has a 16.5 per cent chance of developing invasive mole, a 2.5 per cent chance of developing choriocarcinoma, and an 81 per cent chance of clinical cure. If she is developing some sort of serious trouble, she is more apt to have an invasive mole than a choriocarcinoma and, since the vast majority of our patients in consultation seem to be young primigravidas with no children, it would seem the better part of wisdom to do the least damage possible to the reproductive function, namely, to explore from above and see if there is a local removable nodule, such as was illustrated in Case 20. I know of at least one other instance, a woman in Rochester, New York, who is alive and well and has produced some children following local excision of an invasive hydatidiform mole.

In summary, my philosophy about this particular problem of sequelae of mole, of which invasive mole is one, is that you be as conservative as possible. Only on the basis of disseminated disease that cannot be taken out surgically should a more radical procedure be used.

Dr. Wilson (Closing). Case 20, in which there was local excision of an isolated lesion, has caused us some concern. As this patient is a local one and can be seen once a month, we are not too concerned that we have mismanaged her case even if the local excision does not result in cure. This patient had enormous lutein cysts, in the neighborhood of 15 cm. in diameter each. The occurrence of lactation the second day postoperatively and the disappearance of the lutein cysts by the eighth day constituted, we felt, good clinical evidence that the lesion removed was the only lesion.

The difficulty in diagnosis I do not think needs more discussion. The pathologist can diagnose only what he sees. If he is not given the right tissue to place under his microscope he may come up with the wrong diagnosis.

The question of deported villi being necessary in metastatic lesions in order to make a diagnosis of chorioadenoma destruens interests me considerably for I found it necessary to arbitrate a difference of opinion between my coauthors, Dr. Hunter, like myself a clinician, and Dr. Dockerty, a surgical pathologist. Dr. Dockerty was very insistent on saying that, if the primary lesion was a destruens lesion, it was not necessary to find villi in the metastatic lesion, and Dr. Hunter was just as insistent that it was necessary to note a villous pattern in the metastatic areas. It is interesting to note, therefore, that both Dr. Hertig and Dr. Dockerty feel that it is not necessary to have a villus in a deported lesion in order to make a diagnosis of chorioadenoma destruens in metastatic lesions.

As to the need for treatment in these patients with a built-in regressive mechanism, study of all of our cases shows that a number had evidence of metastasis which we did not treat, mainly on the basis that the level of gonadotropin was falling and that there was no evidence of extension of the primary or metastatic lesions. It is a real problem as to whether or not some patients should be treated with x-ray or other therapy. My worry, as a clinician, is that I have a patient who has a lesion which, if not treated, can perforate and cause severe, and perhaps fatal, hemorrhage.

Lesions of the circulatory system of the placenta

A study of 234 placentas with special reference to the development of infarcts

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CIRCULATORY lesions of the placenta have been designated by a variety of terms with a diversity of opinion regarding their origin and development. Much of this confusion has resulted from a lack of knowledge, until relatively recently, regarding normal circulation of the placenta. The work of many investigators has led to the present concepts of circulation of the placenta, as summarized by Ramsey.¹

About 100 endometrial spiral arteries connect with the placenta (Fig. 1). These split into a number of terminal branches before entering the intervillous space. The maternal veins also open out of the intervillous space at more or less regular intervals. Maternal arterial blood enters the intervillous space through the basal plate and is directed upward toward the chorionic plate. The force of this fountain of blood is slowed as it traverses the intervillous space because of the change in the shape and volume between the maternal arterial system and the intervillous space and because of the obstruction offered by the villi. Gradually the force is spent, and lateral and downward flow of blood to the orifices of maternal veins is accomplished. The pulsation of the chorionic villi and the intermittent contractions of the uterus aid in the stirring and mixing of the maternal pool of blood. There is intercommunication of blood flow between cotyledons. The marginal sinuses, or marginal lakes, may act as safety reservoirs to cope with temporary overfilling of the placenta, resulting from abnormal access of blood or impeded drainage.¹

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The chorionic villi depend into the intervillous space from the chorionic plate. The treelike ramifications of the villi contain the fetal arteries and veins, and in the twigs there is the all-important capillary bed.

The orifices of the maternal vessels can be demonstrated by histologic examination of the basal plate (Fig. 2). The arterioles can usually be distinguished by their slightly thicker walls and sometimes by the presence of several cross-sections because of the spiral configuration of the arteries (Fig. 3). The veins have thinner walls and the lumina are often flattened.

From this concept of placental circulation, it is reasonable to anticipate several sites of interference with normal circulation, namely, in maternal arteries, in maternal veins, in both maternal arteries and veins, and in fetal arteries and veins.

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Method of study of current material

All placentas delivered at the Coleman Hospital on 2 days of each week for a pe-

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Presented at the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960.

riod of 4 months were examined. In addition, on other days of the week the placentas from pregnancies in which there was a pathologic process prenatally, during labor, or during delivery were also examined. A total of 234 placentas were studied. For purposes of statistical frequency, a selected group of the last 100 was used. The earlier cases were excluded because the method of examining the placentas was not uniform. The placentas were examined externally in the fresh state within 12 hours after delivery. They were then fixed in 10 per cent neutral formalin for a period of 1 to 3 days. This preliminary fixation aided in cutting the placentas into strips 1 cm. thick without distorting the tissue. Sections were taken of all lesions. If no lesions were seen grossly, at least one section was taken of the placenta and one of the umbilical cord. Many lesions were serially blocked to demonstrate maternal vessels. The sections were stained with hematoxylin and eosin routinely. Selected sections were stained by McManus's periodic acid-Schiff, Laidlaw's reticulum, or Masson's trichrome methods.

Findings

Intervillous fibrin deposition was found in varying degrees in all 100 placentas used for the statistical analysis. There were 37 in which this was the only pathologic finding. A total of 137 other lesions were found in the remaining 63 placentas. It was frequently not possible to differentiate between the types of lesions grossly.

1. Intervillous fibrin deposition. In all of the placentas delivered during the late third trimester or at term, fibrin deposition in the intervillous space was present (Fig. 4). This was found in the sites where circulation of maternal blood was slowed, especially beneath the chorionic plate (Langhan's membrane) (Fig. 5), on the surface of the decidua (Rohr's membrane), and at the margins of the placenta (Fig. 6). In addition, foci of intervillous fibrin deposition often surrounded a single villus or groups of villi. Because the enmeshed villi were separated from the maternal blood in the intervillous space, the involved villi were necrotic. Proliferation of cytotrophoblasts at the borders of the lesions was usually found.

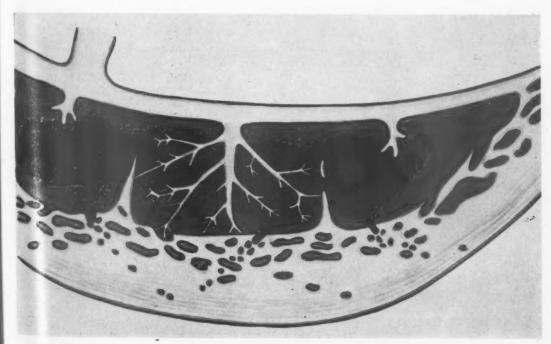


Fig. 1. Diagram of placental circulation.

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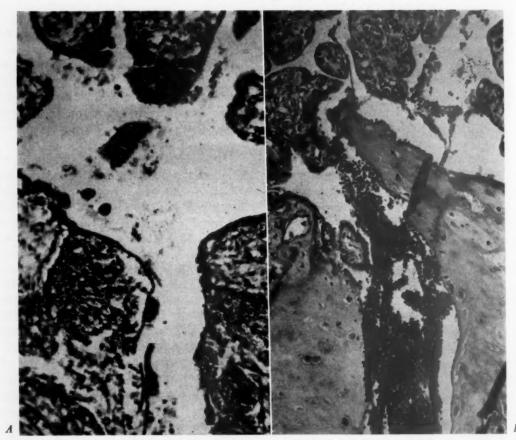


Fig. 2. Orifice of maternal arteriole at the intervillous space. A, Five months' gestation; B, term.

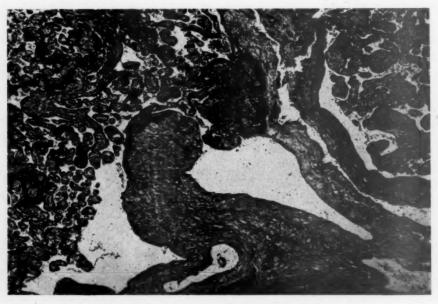


Fig. 3. Venous sinus at the margin of cotyledon.

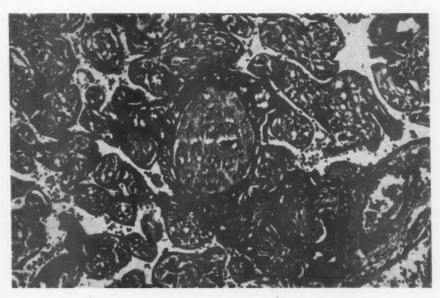


Fig. 4. Intervillous fibrin deposition. The villus is encased in fibrin.



Fig. 5. Fibrin deposition along the chorionic plate (Langhan's layer).



Fig. 6. Fibrin deposition on the decidual plate (Rohr's stria).



Fig. 7. Gross appearance of infarct resulting from obstruction of maternal arteriole.

These lesions probably resulted from foci of slowed circulation or eddy currents in the intervillous space.

2. Infarct, resulting from obstruction of a maternal artery in the decidual plate. In the 100 placentas, 37 lesions of this type were found. Usually, only one such lesion was found in a placenta, but occasionally several were present. In one placenta, 6 lesions of this type were seen.

The lesion grossly was round or oval in. outline with well-demarcated borders (Fig. 7). It was almost always in contact with the decidual plate. The lesion varied from red to white and was firm (Fig. 8). Histologically, the villi in the involved area converged, with a decrease in the amount of the intervillous space because of the loss of the arterial pressure with continued patency of the veins (Fig. 9). The fetal vessels were engorged in the early state. Later, the villi were necrotic. The viability of the villi is dependent upon a patent intervillous space with circulating maternal blood (Fig. 10). The border between this lesion and the



Fig. 8. Infarct produced by thrombus in a maternal arteriole in the decidual plate.

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Fig. 9. Moderate magnification illustrating thrombus in the maternal arteriole and part of the infarct.

adjacent chorionic villi was usually sharp. The villi at the margins of the lesion often were encased in fibrin, but little fibrin was present in the intervillous space elsewhere in the lesions. Proliferation of cytotrophoblasts at the margins of the lesion was noted (Fig. 11). Necrosis of the decidual plate in contact with the lesion was found, and a maternal artery filled with thrombi was usually demonstrated (Fig. 12).

3. Intervillous thrombus, probably the result either of obstruction of a maternal vein in the decidual plate or of the venous outflow tract. This type of lesion was encountered in 92 instances. As many as 20 such lesions were found in one placenta but usually less than 3 were seen.

The lesion presented as a defect in the intervillous space (Fig. 13). Sometimes the space was filled with liquid blood, but more often it was occupied by a red thrombus with white lines of Zahn or by a laminated, decolorized thrombus. The consistency varied from soft to firm, depending upon the stage of the lesion.

Histologically, the lesion lacked villi and was composed of the thrombus in various

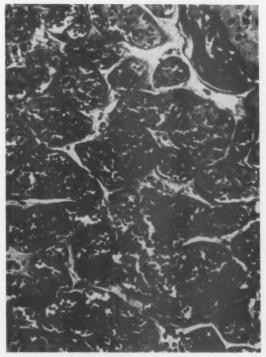


Fig. 10. Congested villi in the central portion of a recent infarct.

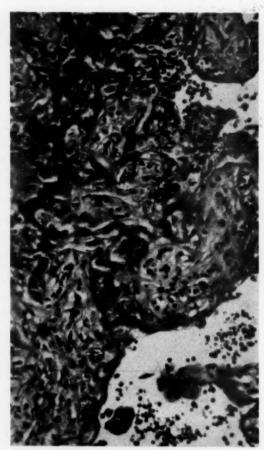


Fig. 11. Fibrin deposition and trophoblastic proliferation at the margin of a recent infarct.

stages of change (Fig. 14). The borders were irregular and were composed of fibrin alone, villi encased in fibrin, convergent villi, or normal villi. In some instances, a thrombus was found in the adjacent maternal vein. In some of these lesions, obstruction of the maternal vein was not found. Probably in these lesions the obstruction to venous outflow was at the mouth of the maternal vein, or even at some distance from the orifice within the intervillous space.

4. Partial premature separation of the placental site, resulting in maternal arterial and venous interruption. This type of lesion was found in 2 of the 100 placentas. The lesion is seen only in placentas which are retained for several days following the separation. Hemorrhage into the decidual plate extending into the intervillous space was present (Fig. 15). Histologically, the villi tended to remain separated, differing from the appearance of the placenta following arterial occlusion, since in placental separation the venous drainage is also interrupted (Fig. 16). The intervillous space sometimes contained fibrin, and the nuclei of some cells in the villi were pyknotic.

5. Fetal vessel thrombosis. This type of

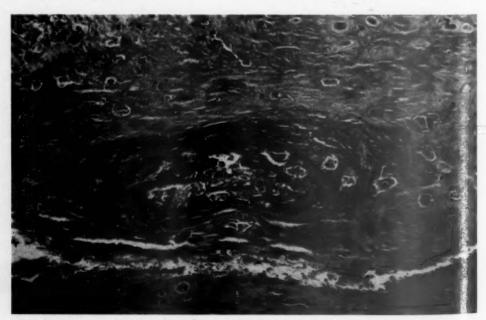


Fig. 12. High magnification of thrombus in maternal vessel.

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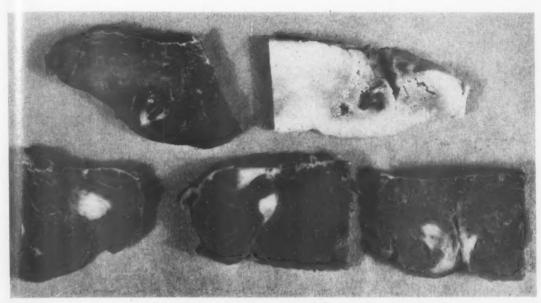


Fig. 13. Gross appearance of intervillous thrombus resulting from venous obstruction.

lesion was encountered in 6 of the 100 placentas. In one instance, the mother had diabetes, but, in the other 5, it was not associated with eclampsia, diabetes, or erythroblastosis. Velamentous insertion of the umbilical cord was present in one of these placentas, but a thrombus was not found in a vessel in the membranes. The site of thrombosis of the fetal vessel was usually one of the major branches of a villous stalk. Grossly, the involved area was pale and sharply demarcated from the adjacent normal placenta (Fig. 17). Histologically, a thrombus in various stages of organization was found in a vessel of the villous stalk (Fig. 18). There was obliteration of the lumina of vessels in the peripheral branches of the villous stalk (Fig. 19). The normal distance was maintained between the involved villi, and the intervillous space was patent. Trophoblastic cells and stroma of the villi remained viable unless the villi were subsequently encased in fibrin. In older lesions there was a deposit of fibrin on the surface of the villi, probably following loss of elasticity of the villi. The villi remained viable unless encased in fibrin. A similar change was found diffusely in those placentas delivered some time after intrauterine death of the fetus and cessation of fetal vessel circulation if the placental site remained intact (Fig. 20).

Comment

The types of lesions observed and the associated vascular obstructions are in keeping with the present-day concepts of placen-



Fig. 14. Intervillous thrombus. A maternal vein in the decidual plate contains a thrombus.

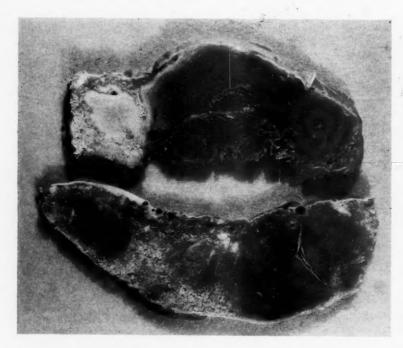


Fig. 15. Gross appearance of partial premature placental separation.

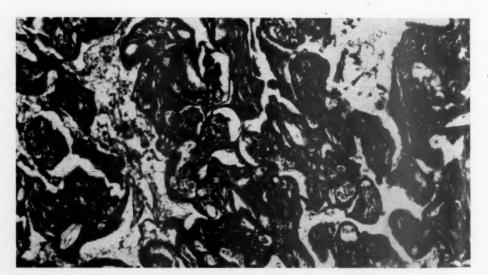


Fig. 16. Villi overlying an area of premature separation of the placental site.



Fig. 17. Gross appearance produced by thrombosis of fetal vessel in villous stalk.

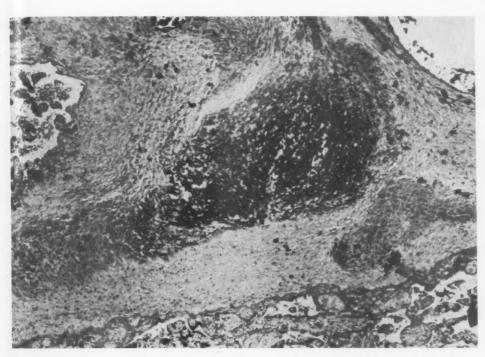


Fig. 18. Occluded fetal vessel in a villous stalk. The vessel is filled with a partially organized thrombus.

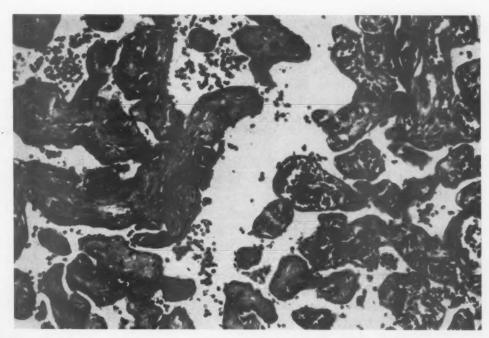


Fig. 19. Effect of occluded fetal vessel in a chorionic stalk. The villi with inapparent vessels are those supplied by the occluded fetal vessel.

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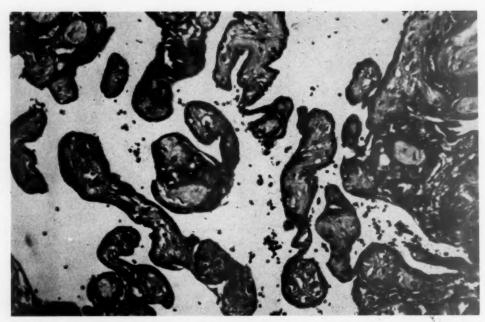


Fig. 20. Intrauterine death. The vessels in the villi are inapparent. Fibrin encases some villi-

tal circulation. These findings add further evidence that such concepts are correct. It is of interest that these lesions may be encountered in the absence of eclampsia, preeclampsia, and other diseases in either the mother or the fetus.

The demonstration of thromboses in major fetal vessels is also of interest. These thrombi, usually in the major branches of villous stalks, resulted in no detected deleterious effect on the fetus. We have not seen previously reported instances of such fetal vessel thrombosis.

Summary

Lesions of the circulatory systems of the placenta have been studied in a series of placentas delivered during the third trimester of pregnancy or at term. Five types of lesions were recognized in the 100 placentas used for statistical frequency:

- 1. Intervillous fibrin deposition was encountered in varying degrees in all of the placentas studied. The lesion is found in areas of the intervillous space where the circulation would tend to be slow.
- 2. Thirty-seven infarcts resulting from obstruction of a maternal artery in the de-

cidual plate were seen. There was usually only one in a placenta, but occasionally several such lesions were present.

- 3. Ninety-two intervillous thrombi were found. Sometimes multiple lesions of this type were present, but usually less than 3 were present in a placenta. The lesion is probably due to slowed eddying currents in the intervillous space as a result of obstruction of maternal veins in the decidual plate.
- 4. A lesion following partial premature separation of the placental site was found in two of the placentas. This lesion is due to separation of both maternal arterioles and veins in the decidual plate.
- 5. Fetal vessel thrombosis involving a major villous stalk was encountered in six of the placentas. A diffuse lesion of the same type is seen in the placenta following intrauterine death.

The lesions demonstrated and the points of obstruction of the circulation are consistent with current concepts of placental circulation.

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Discussion

DR. EDWARD C. HUGHES, Syracuse, New York. Drs. Huber, Carter, and Vellios have carefully studied the vascular changes in 243 placentas and have observed 5 different types of lesions. Their findings emphasize again the vast number of histologic changes which may occur in this organ without apparent effect upon the growing fetus. If such an effect is to be judged simply by the fact that the fetus is born alive, this statement is in general true. However, it is difficult to believe that such vascular lesions, no doubt interfering with the transfer of nutritive materials, would not have some subtle effect upon the fetus.

There is no organ or neoplasm in the human or animal body where vascular proliferation occurs so rapidly. The anatomic relationship between the placenta and decidua makes it almost predictable that some natural histologic changes may develop in the placenta. Lesions are found more often when pregnancy is complicated by diabetes, toxemia of pregnancy, and syphilis. In these listed conditions there is a generalized vascular disease, and the decidual-placental relationship in the uterus is altered in the same manner.

Many investigators have observed by direct measurement that this physiologic rhythm of the uterus is important for decidual circulation. It has also been noted that, when pregnancy is complicated by such things as toxemia of pregnancy and diabetes and in prematurity, the normal rhythm of the uterus is disturbed. It has been recorded that circulation within the intervillous spaces is also altered at the same time. Bruns and others have recorded, by the disappearance of labeled sodium chloride and by demonstration of the hypertonicity of the uterus, that uterine circulation is reduced in cases of premature labor. Although the authors have not actually stated that these placental changes have occurred when these complications were found, others have noted by careful inspection of the placenta that they do occur more often when these complications are present.

It has been stated that many of the changes which occur in the normal placenta are due to the fact that the placenta is becoming senescent. Although some have stated that the maximum function of the placenta occurs at approximately 36 or 37 weeks of gestation, more recent intricate work concerning the actual metabolic activity of this organ seems to question these assertions.

The recent work of Roux and Villee concerning the metabolism of the placenta seems to indicate that the placenta remains metabolically active until term. In our own laboratory transplantation of portions of term placenta into the anterior chamber of the rabbit's eye indicated that term placentas have the ability to grow and produce hormones. Placental growth, particularly of the cellular components of the placenta, was greater when portions of placentas from diabetic, toxic, or Rh-negative patients were implanted.

The authors have described 6 different types of vascular lesions in the placentas which they have studied. The most frequently observed one was the deposition of intervillous fibrin in varying degrees. This substance was found in all the placentas studied. This important finding has been the subject of considerable discussion by other observers, and some questions have been raised. The first question which might be asked was whether the deposition of this substance both within and surrounding the villi was actually the result of vascular lesions. The second question which could be raised was whether this substance was actually fibrin in nature or whether it represented the accumulation of some substance resulting from failure of synthesis at the decidual-syncytial level. Specific histochemical staining of this material suggested that it might be a glycoprotein rather than fibrin. Special staining of these areas for alkaline phosphatase -an enzyme involved in the transfer of such materials across the placenta-indicated that the amount of this enzyme is decreased and in some areas is entirely absent. A third question which could be discussed is whether the deposition of this material in the placenta in any way could be related to the metabolic status of the mother and/or the fetus. Accumulation of a similar substance can be noted in the glomeruli of the maternal kidney in toxemia of pregnancy and also in the lung of the newborn infant who is developing hyaline membrane disease. Some similarity of action can be visualized inasmuch as both the glomeruli of the kidney and the aveolar spaces of the lungs are closely related to capillary function and the transfer of materials to and fro across these capillary margins. In the toxic kidney this material seems to accumulate between the basement membranes of the cells of the capillary tufts. However, in the lung of the newborn, the eosin staining material seems to cover the alveolar spaces and also may involve the capillaries of the lungs. Lesions of the pla-

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centas are noted quite regularly when these complications are present.

Dr. R. A. Bartholomew, Atlanta, Georgia. There is an old Chinese proverb stating that a picture is worth a thousand words. I think it applies particularly well to the subject now under discussion.

Dr. Huber has properly emphasized the circulation in the placenta because it has much to do with the lesions that have been found. If I am not mistaken he also emphasized that infarcts are due to thrombosis in decidual maternal arteries.

I would lay greater stress on the fact that infarction of the placenta begins with obstruction in the fetal circulation and secondarily involves the intervillous circulation.

In describing the placental circulation I must take issue with the view that seems to prevail at the present time. It has been promulgated mainly by Elizabeth Ramsey. She and I have had a great deal of friendly correspondence about this difference in viewpoint, namely, that blood entering the basal plate through the decidual arteries courses upward in sinusoidal fashion, which insures villi proper nourishment. If blood cannot get to villi in one direction it can do so from another direction. Impelled by the maternal blood pressure it reaches the chorionic plate.

At this point our views diverge. Her concept holds that the direction of the flow is reversed and that the blood "falls back" to the basal plate viens. Does it seem reasonable that a flow which is under the influence of maternal blood pressure could reverse its direction and "fall back" against the ascending blood? It seems unreasonable to me.

I would remind you also that we see clinical evidence of dispersal of the blood to the periphery of the placenta into the marginal sinus, thence into connecting links into the deeper uterine veins.

Rupture of the marginal sinus can create such an amount of hemorrhage that it often calls for several units of blood to replace the loss. If the marginal sinus were merely a useless passage that received only a limited amount of blood, it would hardly explain a large accumulation of clot connected to the sinus by a thrombus extending through a rent in sinus wall.

The infarcts can be labeled according to various criteria. Unless one fixes the placenta for 3 or 4 weeks, the fixation is not complete throughout the thickness, and a lesion may not

have uniform color. The slides shown depict a variety of lesions. As yet, a really descriptive name cannot be applied to each, hence we have followed the plan for vitamins terming them A, B, C, D, E, F, G, and H.

The most significant infarct is the one 1 r. Huber terms No. 2. It is the one which is associated with toxemia, and has the typical black appearance due to thrombosed intervillous blood. If the pregnancy is not interrupted for some time the color changes to brown as the hemoglobin deteriorates. Accumulation of fibrin between villi is induced by thromboplastin which is liberated when hypoxia causes early necrosis of chorionic epithelium. It is possible for the No. 2 type of infarction to develop during labor, giving rise to proteinuria and moderate hypertension late in labor and for 12 to 24 hours following delivery.

DR. ARTHUR T. HERTIG, Boston, Massachusetts. Dr. Huber has presented very clearly this morning his views about general circulation in the placenta. I think perhaps my point of view about the circulation of the placenta is a combination of Dr. Ramsey's and Dr. Bartholomew's, namely, that the arterioles enter at the base of the cotyledon, usually near the center. When you look at them grossly or dissect them, there is some venous drainage at the margin of the cotyledon and that venous drainage is analogous in location anatomically and in size and proportion to the venous drainage at the margin of the placenta to which Dr. Bartholomew referred. Hence we have circulation within the individual cotyledon as a sort of slow arching fountain and some of the blood flows over the top of the septum and a good deal of this overflow accumulates at the marginal sinus. These lesions, which have been described so beautifully by Dr. Huber are really a sequel to this concept of the circulation.

I would like to comment only briefly on what Dr. Huber said about the role of the fetal circulation. It is my belief that the viability of the villus is a function of the maternal circulation. The best example of that is that, in the hydatidiform mole, which has no circulation, there is usually not any necrosis of the villus. When one looks at these true infarcts, and by "infarct" we mean dead tissue, there is demonstrable thrombus in the maternal arterial supply, as Dr. Huber had indicated. He has also indicated what we have seen many times, that when the baby

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dies the placenta does not become infarcted but simply the vessels are thrombosed and involuted. We were taught in medical school that thrombosis is of two sorts: antemortem and postmortem. We were taught that only the antemortem type undergoes organization with ingrowth of fibroblasis. Only in the placenta of the dead baby or in the placenta of the localized thrombosed fetal circulation do we find organization of what is essentially a postmortem thrombus. This is the only exception to the general dictum of no organization except in an antemortem clot. Hence it is my belief, based on having seen a good many placentas and studying them carefully, that obstruction of the fetal circulation, although it produces sequelae of ischemia and loss of vessels, does not result in necrosis of the placental tissue.

Dr. Huber (Closing). The lesions we have attempted to describe are consistent with the concept of the placental circulation which we believe is the background for their development. It seems to me that the injection experiments of Dr. Ramsey and others lend very definite support to the assumption that there is a venous drainage throughout the entire decidual plate and that the marginal sinuses play a much less important part in the total circulation than has been assumed in the past.

I am grateful to Dr. Hertig for pointing out that the viability of the villi depends largely on the maternal circulation and not on the integrity of the fetal circulation. It was our feeling that in these localized lesions associated with thrombus in the fetal vessel the absence of circulation made the villus a little more rigid so that there was more chance for it to have fibrin deposition around it, and that as it became encased in fibrin then the maternal circulation no longer nourished the villus and it became necrotic.

Choriocarcinoma

A report of the 5 or more years' survival from the Albert Mathieu Chorionepithelioma Registry* **

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FOR many years the concept generally has been held that patients with choriocarcinoma rarely, if ever, survived. It has been contended that if the patient lived the correct diagnosis was not choriocarcinoma.1 There has been some relaxation of this rigid thought but there still remains the suspicion in the minds of many that the diagnosis of choriocarcinoma is inaccurate if the patient survives. Novak and Seah2 dispelled this to some extent with their report of the Registry material in which 13 of 74 patients with choriocarcinoma remained well, 11 of them for over 2 years and 2 over one year. In a report by The Joint Project for the Study of Choriocarcinoma and Hydatidiform Mole in Asia3 Iverson presented the following survival figures as calculated by the actuarial method: of the 57 Asian pa-

tients with choriocarcinoma 18.7 per cent survived for 2 or more years; of the 17 U. S. patients 39.2 per cent survived 2 or more years. lo

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Five-year survival data are difficult to acquire because of the infrequency of choriocarcinoma and because of the limited number of cases studied by a single group. Thus, the principle source of material from which to compute long-term survival data is the individual reports in the literature, a source that does not always present convincing evidence of the accuracy of the diagnosis of choriocarcinoma. Isolated cases of survivals of 5 or more years have been reported.4-13 Brews14 reviewed the records of the London Hospital from 1885 to 1937 and found that 8 of 24 women with choriocarcinoma had survived 5 or more years. Smalbraak¹⁵ reported that 7 of 17 patients had survived for 6 to 24 years.

The material accumulated in the Albert Mathieu Chorionepithelioma Registry provides an excellent opportunity to evaluate 5 year survivals since the number of cases is large and since the clinical histories and the pathologic material have been studied by one group over a period of many years. It is accepted that the figures under consideration are biased since all known cases of trophoblastic lesions have not been registered and since the cases forwarded to the Registry have been selected to some extent.

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Presented at the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960.

*Maintained by a grant from the Obstetrical and Gynecological Assembly of Southern California.

**Aided by a grant from the Robert C. Ziebarth Research and Educational Fund.

***Aided by the Josiah Macy, Jr., Foundation Fellowships in Reproduction for medical students. For example, one case of choriocarcinoma was sent specifically because of the patient's long survival. Despite this bias, some information can be gained.

Material

The Registry, as of Aug. 1, 1958, contained the clinical data and pathologic material of 21 patients with choriocarcinoma who have survived without evidence of disease for 5 or more years after treatment was instituted. A study of these including the accuracy of the diagnoses form the basis of this report. The complete material in the Registry on this date consisted of 530 specimens of suspected or actual trophoblastic growths, of which 147 were classified as choriocarcinoma by the Committee. Of these 147 patients 95 have died of the disease.

Results and comments

The 21 patients who have survived 5 or more years. The lengths of time these 21 patients have survived without evidence of disease are: 5 patients for 5 years (Cases 12, 14, 15, 17, 18); 3 for 6 years (Cases 5, 6, 7); 6 for 8 years (Cases 1, 9, 10, 13, 20, 21); 1 for 9 years (Case 8); 3 for 10 years (Cases 3, 4, 11); 1 for 12 years (Case 2); 1 for 15 years (Case 16); and 1 for 34 years (Case 19).

The basic treatment in the 21 cases was hysterectomy in 20 and laminectomy for a metastatic lesion in one. In 5 instances the ovaries were not removed; 3 of these patients have survived without evidence of disease for 6 years and 2 for 8 years.

Six of the 21 patients had metastatic lesions. In 3 (Cases 13, 18, 21) the lungs were involved, demonstrated by x-ray examination in 2 cases and by lobectomy and histologic examination in one (Fig. 1). The latter patient is living without evidence of disease 8 years after hysterectomy and lobectomy. Of the other 2, one is living and well without evidence of disease 8 years after hysterectomy, bilateral salpingo-oophorectomy, and roentgen therapy to the lungs, and one has survived without evidence of

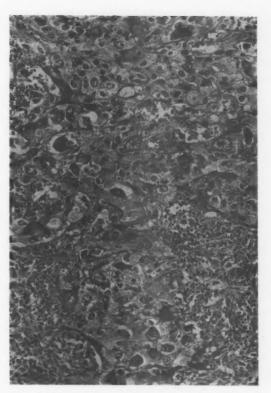


Fig. 1. Metastatic choriocarcinoma in the lung. Survival without evidence of disease for 8 years after hysterectomy and lobectomy (Case 21).



Fig. 2. Choriocarcinoma in myometrium (Case 3).

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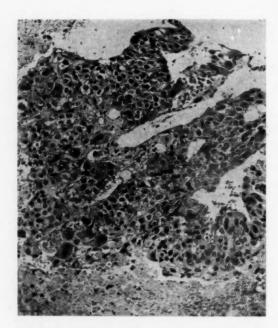


Fig. 3. Metastatic choriocarcinoma in vaginal wall (Case 3; see Fig. 2). Survival for 10 years without evidence of disease.

disease for 5 years after hysterectomy. The pulmonary lesion regressed without specific therapy. One patient (Case 3) with a vaginal metastasis has survived 10 years following hysterectomy, bilateral salpingooophorectomy, and excision of the vaginal lesion (Figs. 2 and 3). One patient (Case 11), in whom a metastatic lesion in the cervix (Fig. 4) was discovered and removed 2 months after supracervical hysterectomy for a hydatid mole, has survived 10 years. One patient (Case 20) has survived 8 years and has had 2 normal pregnancies after a laminectomy and roentgen therapy for choriocarcinoma metastatic to the spine (Fig. 5). (Two years and 5 months previous to the discovery of the choriocarcinoma this patient had had a hydatid mole. Biologic pregnancy tests were done 2, 5, and 19 months after evacuation of the mole. The last one was performed 6 months before the patient developed back symptoms and 9

Table I. Diagnoses in the 21 patients surviving 5 or more years*

Case No.	Choriocarcinoma	Chorio- adenoma destruens	Benign mole	Placental tissue, not ma- lignant	Syncytial endo- myometritis	No tropho- blast present	No diagnosis	Meta- static syncytia tissue
1	1, 2, 3, 4, 6, 7, 12		_			,		
2	1, 2, 3, 4, 6, 7, 12			10		P		
3	1, 2, 3, 6, 7, 12	10						
4	1, 2, 3, 4, 6, 12	7, 10						
5	1, 2, 3, 4, 6, 12	7,10						
2 3 4 5 6 7 8 9	1, 2, 3, 12	7, 10						
7	1, 2, 3, 6, 8, 10, 12					7		
8	1, 2, 3, 6, 7, 8, 12		10					
9	1, 2, 3, 4, 12	10			7			
	1, 2, 3, 6, 9, 11, 12	4		7				
11	1, 2, 3, 4, 6, 9, 12			7				
12	1, 2, 3, 6, 10, 12	. 4, 7						
13	1, 2, 3, 4, 6, 7, 10, 12							
14	1, 2, 3, 6, 9, 12	4, 7			10			
15	1, 2, 3, 4, 5, 12			10	7			
16	1, 2, 3, 12		4,7	10				
17	1, 2, 3, 12	7					10	
18	1, 2, 3, 7, 12	10						
19	1, 2, 3, 12			7, 10				
20	1, 2, 3, 10, 12							7
21	2, 3, 7, 10, 12							

*Each examiner was assigned a number which appears under the diagnoses made by him. Each examiner did not see all cases.

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months before the laminectomy. All were positive. No uterine lesion was detected. After the laminectomy, removal of the metastatic lesion and roentgen therapy the tests became negative.)

The question of accuracy of diagnosis. Long-term survival of patients with choriocarcinoma always poses the question of the accuracy of the diagnosis. Histologic interpretation of the potentialities of trophoblastic activity is notoriously difficult. In some cases the trophoblast in a metastatic lesion may closely resemble benign tissue and yet the patient dies of extensive metastatic choriocarcinoma. In others, the trophoblast in a mole may appear malignant but simple curettage provides a permanent cure. Errors in interpretation may be made if inadequate numbers of blocks of tissue and histologic sections are studied, if the blocks are selected from the wrong portions of the lesion, if too much reliance is placed upon the results of biologic tests and if the experience with these lesions is not broad. Disagreement concerning the diagnosis is rather commonplace.

Using a portion of the Registry material, Park¹⁶ recorded the diagnoses as made by the members of the Committee and presented the following results: In 89 cases where the question of choriocarcinoma arose there was agreement in 30 per cent of the cases, partial agreement in 21 per cent, and disagreement in 48 per cent. He noted that in 35 of the 43 cases in which there was disagreement, sections from the excised uterus were available for examination, which indicated to him the difficulty of diagnosing the lesion, not only from curettings but also from the intact removed uterus.

These various facts, especially the inference contained in Park's report of the Registry material to the extent that the diagnoses were not very accurate, makes it essential to establish firmly the diagnoses of the 21 cases under consideration if these long-term "cures" of the disease are to be authenticated.

The diagnoses made by the examiners in these 21 cases were tabulated to determine

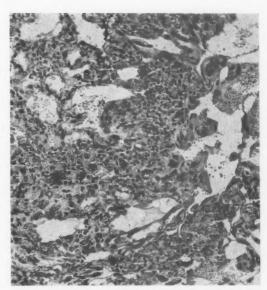


Fig. 4. Metastatic choriocarcinoma in cervix. Survival for 10 years without evidence of disease (Case 11).

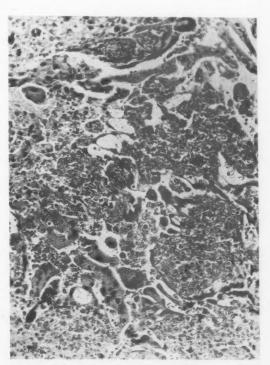


Fig. 5. Choriocarcinoma of vertebra. Survival without evidence of disease for 8 years during which time the patient has had 2 normal pregnancies (Case 20).

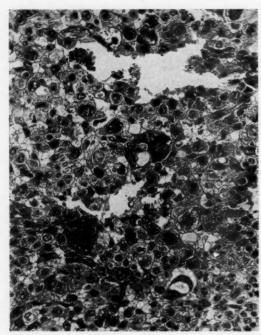


Fig. 6. Choriocarcinoma deep in myometrium (Case 10). Patient living without evidence of disease for 8 years.



Fig. 7. Choriocarcinoma in myometrium (Case 9). Survival for 8 years without evidence of disease.

the extent of agreement in a manner similar to that used by Park. This revealed a high rate of disagreement just as his findings did. There was unanimous agreement in only 3 and disagreement in 18.

The disagreement was so prevalent that we believed there might be extenuating curcumstances leading to the variety of opinions and that, possibly, the simple listing of the diagnoses was inadequate to portray the actual situation. There are two points which conceivably might be pertinent: (1) consideration of which examiners were in disagreement and (2) consideration of the basis upon which the diagnoses were made by each of the examiners.

The examiners consisted of 5 Fellows of the American Association of Obstetricians and Gynecologists who served on this Committee for several years. Each interpreted the clinical data and pathologic material entirely independently of the others. Occasionally, consultation was obtained from pathologists not on the Committee. During the existence of the Registry, 11 gynecologists and/or pathologists have examined the material and made diagnoses. To make a detailed analysis of the diagnoses, each of the 11 examiners was given a number. Number 12 was assigned to the pathologist at the hospital from which each of the specimens came. The number of each examiner and his diagnosis were then listed in table form (Table I). All examiners did not study each of the cases so not all 12 numbers appear for each case.

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The majority of those who examined the 21 cases made the diagnosis of choriocarcinoma in each instance (Table I).

Further survey of Table I reveals that the disagreement was accounted for by two examiners and the same two frequently differed between themselves. A third examiner was involved in 4 cases.

The most frequent disagreement was between choriocarcinoma and chorioadenoma destruens. This was true in 10 cases (Cases 3, 4, 5, 6, 9, 10, 12, 14, 17, 18). By definition, the pathologic criteria of chorioadenoma destruens are abnormally deep penetration

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into the myometrium and adjacent structures of molar tissue, both trophoblast and formed molar villi, and abnormal degrees of trophoblastic proliferation. An evaluation of the pathologic material in these 10 cases brought out the fact that no villi were present and that the lesion in each case was composed solely of abnormal proliferating trophoblastic tissue which had penetrated deeply into the myometrium (Figs. 2, 6, 7, 8). Without villi it is impossible to accept the diagnosis of chorioadenoma destruens. Of course, it is possible for a histologic section to be cut tangentially in such a manner that the villous structure could be missed and this would be especially true if only few sections were made of the surgical material. But this would not account for the diagnosis of chorioadenoma destruens in these particular 10 cases since a diligent search failed to reveal villous structures of any type.

In 2 cases (Cases 8, 16) the diagnosis of "benign hydatid mole" was made despite the fact that in neither case were there villi of any type in the pathologic sections. The pathologic criteria of hydatid mole are trophoblastic proliferation, hydropic degeneration of the villous stroma, and scantiness of blood vessels in the villi. In these 2 cases the marked and deep invasion of the myometrium by trophoblast, the excessive proliferation and anaplasia of the trophoblast, the hemorrhage, the necrosis, and the absence of hydropic villi fulfill the criteria for the diagnosis of choriocarcinoma, not benign hydatid mole.

In 6 instances (Cases 2, 10, 11, 15, 16, 19) the diagnosis of "trophoblast, not malignant" was made. It is certainly accepted that it is difficult to determine with accuracy from histologic sections the malignant character of trophoblast in all instances but the preponderance of opinion in these 6 cases is for choriocarcinoma since in 3 there were 7 examiners who called the lesion choriocarcinoma, in one there was 6, and in 2 there were 4 (Table I). Photomicrographs of 5 cases are presented for review (Figs. 4, 6, 9, 10A, 10B, and 11). The sixth (Case

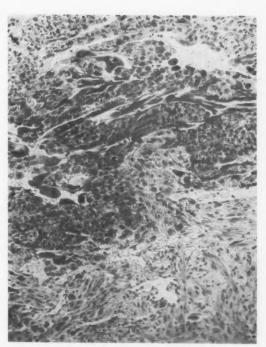


Fig. 8. Choriocarcinoma in myometrium (Case 14). Survival for 5 years without evidence of disease.

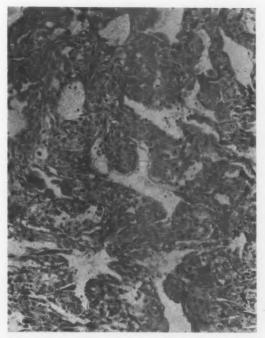


Fig. 9. Choriocarcinoma in myometrium (Case 2). Survival for 12 years without evidence of disease.



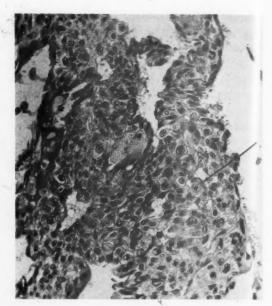


Fig. 10A. Low power photomicrograph to show choriocarcinoma in myometrium.

Fig. 10B. Higher power to show character of the mitoses (arrow) trophoblast (Case 15). Survival without evidence of disease for 5 years.



Fig. 11. Choriocarcinoma in myometrium (Case 19). Survival without evidence of disease for 34 years.

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In 3 cases (Cases 9, 14, 15) the diagnosis of "syncytial endomyometritis" was made by a single examiner, although in each case there were abundant masses of cytotrophoblastic tissue present in the lesion. Eight examiners observed-masses of syncytium and cytotrophoblast in one case (Case 14), 6 diagnosing the lesion as choriocarcinoma and 2 as chorioadenoma destruens, the latter even though no villi were present (Fig. 8). In the other 2 instances (Cases 9, 15), 6 and 7 examiners, respectively, observed masses of cytotrophoblast (Figs. 7, 10A, and 10B). Hemorrhage and necrosis of the myometrium were prominent in all 3 cases. The pathologic criteria of syncytial endomyometritis are invasion of the endometrium and myometrium by syncytial cells which tend to infiltrate along tissue spaces, rarely accompanied by cytotrophoblast, and seldom associated with hemorrhage and necrosis of the material tissues as is chorio-

carcinoma. Masses of cytotrophoblast, hemorrhage, and necrosis in these cases negate a diagnosis of syncytial endomyometritis.

In one case (Case 7) the diagnosis of "no trophoblast" was made by one examiner but a study of the sections reveals considerable syncytium and cytotrophoblast sufficient in amount, character, and location to induce all the other 7 examiners to make the diagnosis of choriocarcinoma (Fig. 12).

The diagnosis of "no diagnosis" was made in one case (Case 17) by one examiner. The sections contain a large amount of malignant-appearing trophoblast which 4 examiners believed sufficient for the diagnosis of choriocarcinoma (Fig. 13) and one thought adequate for the diagnosis of chorioadenoma destruens; the latter even though no villi were present.

In one case (Case 20) the diagnosis of "syncytial tissue, metastatic" was made by one examiner while the other 5 found enough cytotrophoblast accompanying the syncytium to diagnose choriocarcinoma (Fig. 5).

It is apparent that the disagreement is not as real as appears and that the simple listing of the diagnoses is not adequate to determine the percentage of accuracy with which the diagnosis of choriocarcinoma was made by the Committee members. There are extenuating circumstances. With proper consideration of these it is possible to say with certainty that the actual rate of agreement is high and that the diagnosis of choriocarcinoma in these 21 cases is accurate.

Summary

Twenty-one of the 147 patients with choriocarcinoma registered in the Albert Mathieu Chorionepithelioma Registry have survived without evidence of disease for 5 or more years.

It was believed that a complete study and evaluation of the diagnosis in each of the 21 cases should be made since the diagnosis of choriocarcinoma is often questioned, especially in long-term survivals.

The study leads to the firm conclusion that the diagnosis of choriocarcinoma was reliably established in each case.



Fig. 12. Choriocarcinoma in myometrium (Case 7). Survival without evidence of disease for 6 years.



Fig. 13. Choriocarcinoma extensively involving the myometrium (Case 17). Survival without evidence of disease for 5 years.

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Discussion

DR. ARTHUR T. HERTIG, Boston, Massachusetts. With respect to Dr. Brewer's paper, I spent a good deal of time on the manuscript, especially concerning the histologic material on 20 out of the 21 cases. This contribution proves that there are bona fide cures of true cases of choriocarcinoma, namely, in the order of 14.4 per cent, as shown in the series of 21 out of 147. This condition has always been considered uniformly fatal.

As you know, the late Dr. Ewing said that if any patient with choriocarcinoma survived the diagnosis was not correct. We are all now seeing examples of spontaneous cures of choriocarcinoma with or without proved metastasis. This spontaneous cure again depends on the built-in tendency of trophoblast to involute, whether such trophoblast is from the normal pregnant uterus or the invasive mole or choriocarcinoma. There is the famous case from Nebraska where the patient had a normal delivery and yet had a left lung full of choriocarcinoma proved histologically 18 months later. Nevertheless, she is alive and well 6 or 8 years later after pneumonectomy.

Fortunately, I had a chance to study Dr. Brewer's manuscript and all 21 cases with the exception of Case 8. They are all choriocarcinoma in my opinion, although some are not classic. I tried, in looking over these 21 cases, to arrive at some conclusions as to why this particularly unique group of 21 patients should all be alive 5 to 34 years later. In reading the material I knew all the cases were alleged chorio-

carcinoma and I knew the patients were alive, so I tended to try to disprove the diagnosis. I looked for evidence of the built-in involutionary mechanism of which we have spoken on several occasions. I looked for some peculiar reaction to serve as a clue to the separation of this 15 per cent of curable lesions from the other 85 per cent that seem to kill the patients quite uniformly. I could not with any degree of honesty or assurance come up with any morphologic criteria which would separate the benign sheep from the malignant goats.

We have mentioned that these choriocarcinomas are quite variable and this is a philosophic point that I would like to dwell on. We try to teach the medical students that we all make the great mistake of believing that all rare lesions of a given type look alike. This is quite wrong because the more you see of rare lesions the more you see there is a spectrum of changes in rare lesions just as there is in common lesions. I think we all agree with this so that, although choriocarcinoma in general is pretty standard and it kills the patient quite regularly in 2 years or less, there are those clinically benign variations about which, by virtue of such scholarly studies as this of Dr. Brewer, we are learning more and more.

I might in passing just mention the last few cases. Case 16 was the least impressive as a choriocarcinoma but it is still choriocarcinoma. Case 17 was the most troublesome morphologically in that it was the most anaplastic and the least like trophoblast in the sense of a nice

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as a nominatorphoc and a nice plexiform pattern that we have learned to recognize, and yet it is undoubtedly trophoblast of a very malignant nature. Case 18 shows the most necrosis of any of the 21 but still has coriocarcinoma. Case 19 has local spontaneous involution which is right next to the maternal tissue. Case 20 is the most fascinating of any. This is of the patient with the uterus left in who had

pneumonectomy for metastases and who has produced a normal child or two.

Dr. Brewer (Closing). I sent Dr. Hertig the slides because I wanted him to have an opinion of his own since illustrations in a journal do not permit one to get a very solid opinion. I am delighted that he did agree in all the 21 cases.

Induction of ovulation in the human with human gonadotropins

Preliminary report

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WALTER HERRMANN, M.D.

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ATTEMPTS by various means to stimulate the inactive or refractory ovary are so familiar to all that there is no need to discuss them here even if there were time to do so. A comprehensive review of this subject is to appear shortly.¹

The work to be reported here concerns the stimulation of ovarian activity, including evidence of ovulation, by the intramuscular administration of human pituitary gonadotropin extracts, hereafter to be referred to as HPG.

For at least 10 years it has been apparent that "species specificity" has been a major factor in pituitary-ovarian relationships.^{2, 3} During the 33 years since human chorionic gonadotropin (hereafter designated as HCG) was shown to produce ovulation in small mammals, there have been numerous unsatisfactory attempts to stimulate human ovarian activity by various gonadotropin extracts. Recent evidence of successful species specific gonadotropin extract administration in the monkey and human has been presented by van Wagenen and Simpson⁴ and by Gemzell.⁵

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Presented at the "Work in Progress" Session of the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960. Although ovulation in the Macaca mulatta could be induced occasionally with sheep pituitary extract combined with human chorionic gonadotropin, van Wagenen and Simpson found that, with appropriate dosage of homologous pituitary material, multiple ovulations could be consistently produced in both the prepuberal and the adult monkey.

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In 40 amenorrheic women Gemzell was able to produce menstruation and evidence of ovulation in 29 by injections of HPG and HCG. Of the 11 failures, 8 had either no ovarian tissue or rudimentary ovaries with no germinative tissue. The other 3 had a pathologic response consisting of marked increase in excretion of 17-ketosteroids and corticosteroids. This type of response has also been reported by Keettel, Bradbury, and Stoddard following injections of hog or sheep FSH.

Materials and methods

The extract used for injection in the present series was obtained from human autopsy material regardless of the age or sex of the subject. This was prepared by extracting the lyophilized glands with 40 per cent ethanol and precipitating the extractable material with higher concentrations of ethanol. The precipitate was redissolved, dyalized, lyophilized, and assayed. A later batch (used in J. J.) was further purified

Table I. Clinical and laboratory evaluation of 9 patients included in this study

Patients	No.	Age	Urinary FSH (mµ)	17-Keto- steroids	Vaginal smear	Endometrial biopsy	BBT	Secondary sex
Primary amenorrhed	ž.					9		
Hypopituitary	1	24	< 6.5	10-11 mg. per 24 hr.	<5% cor- nification	No tissue	Flat	Atrophic
Adrenal cortical hyperplasia	1	33	<13	60-80 ā cortisone	0 cornifica- tion	No tissue	Flat	Masculin- ized
Secondary amenorrh	rea							
Hypothalamic or hypopituitary	6	22 to 27	< 6.5	9-11 mg. per 24 hr.	0-5% cornification	None to inactive prolifera-	Flat	Atrophic to normal
Operative control (endometriosis)	1	38				tion Secretory	Normal	Normal

	PT./0	YCLE			DAYS	OF M	EDICAT	ION			RESULTS
KEY	,		1	2	3	4	5	6	7	8	
16000 HCG	D.H.	п									No ovulation (spotting) No ovulation (spotting) No ovulation (spotting)
	S.O.	I	mmm.	ununn	XIIIIIIII	· · · · · · · · · · · · · · · · · · ·					Anovulatory bleeding
dose	A.R.	I		NO NO	HPG HPG						ovulation ovulation
Note All patients were given 9000 u. HCG b.i.d. X 4 as	J.W.	п	unisun. ununn. ununn.								ovulation ovulation Anovulatory bleeding
control injections. One (A.R.) ovulated follow ing this R having regular cycles since	A.P.	m ň I									Anovulatory bleeding ovulation ovulation
,	J.P.	I	///////////////////////////////////////				XIIIIIIIII		MILLION TO STATE OF THE STATE O	. www.	ovulation
	M.J.	I				SUIIIIIII	XIIIIIIII		ennin		ovulation
	J.J.	п									ovulation ovulation ovulation

Fig. 1. Results of treatment (HCG and HPG) in 8 patients.

on an ion exchange column permitting the removal of most of the LH activity and increasing its FSH activity approximately threefold.

Sixteen courses of injections were given to 8 patients as designated in Fig. 1, following a course of concentrated chorionic gonado-

tropin* as a control. Patients were evaluated by means of basal body temperature charts, endometrial biopsy, vaginal smear, in one case culdoscopy, and in another laparotomy.

All patients except the control patient had

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^{*}APL used through the courtesy of Ayerst Laboratories.

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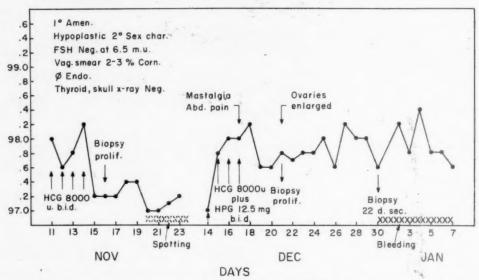


Fig. 2. Basal body temperature graph of Patient J. W. Ovulation probably occurred following administration of HCG/HPG combination.

been amenorrheic either primarily or for from 3 to 6 years. They had various diagnoses (Table I), and all had had the usual endocrine investigations consisting of thyroid studies, sella turcica x-rays, 17-ketosteroid determinations, FSH assays, etc. Many had had previous extensive courses of therapy of one type or another in attempts to cure the amenorrhea. Most of the cases were diagnosed as "hypothalamic" amenorrhea with low estrogen and low FSH excretion. Two were cases of amenorrhea designated as del Castillo syndrome, with amenorrhea, low estrogen, low FSH and galactorrhea. One was a case of congenital adrenal cortical hyperplasia of many years' standing.

As will be seen from reference to Fig. 1, one patient, after 3 years of amenorrhea, ovulated and menstruated after each of 2 courses of HCG alone and, as a matter of fact, has continued to menstruate and ovulate since, a result quite different from all the others. The remaining patients failed to ovulate or menstruate following HCG therapy alone and they therefore were considered appropriate cases to be treated with a combination of HPG and HCG by means of a technique which had been designed

originally by van Wagenen and Simpson⁴ in treating *Macaca mulatta* monkeys. Several variations of therapy were tried at first, however, before what was considered to be the most satisfactory method was established. This proved to be the administration of 10 mg. of HPG twice daily for 4 days followed by 4 days of administration of HPG, 10 mg., plus HCG, 8,000 units, twice daily. Five courses of therapy were given by this technique, all of which produced evidence of ovulation followed by menstruation.

All patients were skin tested and in each case there was a small amount of reaction to the skin test which did not seem severe enough to contraindicate continuing the series, but all injections caused some discomfort for a period of 6 or 8 hours. The variations in therapy before the ultimate most satisfactory technique was used are described in Fig. 1.

Results

Charts of several of the patients quite characteristic of all in the successful series are shown in Figs. 2 and 3.

The endometrium found on biopsy showed

definite secretory changes (Fig. 4) but actually in some cases seemed a little atypical in that there was a more pronounced stomal predecidual reaction than one would expect in a normal menstrual cycle.

One patient, A. P., in whom a former diagnosis of anorexia nervosa was made and who had long-standing infertility was examined culdoscopically after one of the routine courses of treatment. Observation of the ovaries at the time of culdoscopy disclosed them to be enlarged to what was judged to be about three times normal size. They were somewhat irregular in shape and hyperemic and at least three areas were observed on each ovary which were further raised above the surface about 1 cm. in diameter, were dark purplish or bluish red in color, and had a hemorrhagic stoma at the apex of each. These were all judged by the several members of the staff who observed them to be quite characteristic of ovulation points. This finding is quite similar to the observations of van Wagenen and Simpson on the monkey and by Gemzell on the human.

As a control, one 34-year-old multiparous woman who required laparotomy because

of endometriosis consented to have the series of injections so that the ovaries could be observed at the time of laparotomy. Since the patient desired oophorectomy in case hysterectomy was necessary, it was possible to obtain the ovaries for examination. Fig. 5 shows the specimen removed at the time of operation. Both ovaries were enlarged to about three or four times normal size and on the surface of each there were several hemorrhagic areas which were thought possibly to be ovulation points. When the ovaries were incised the enlargement was seen to be due to a number of cystic areas, several of which in each ovary were hemorrhagic and filled with bloody fluid. Fig. 6 shows microscopic sections through some of these areas indicating fresh corpora lutea but, interestingly enough, corpora lutea in different stages of development as determined by the criteria of Corner.7 This may represent ovulation 24 or 36 hours apart. The significance of this is unknown, but it must be remembered that this was a woman who was menstruating and ovulating normally, in whom multiple ovulations were apparently produced by the HPG-HCG injections.

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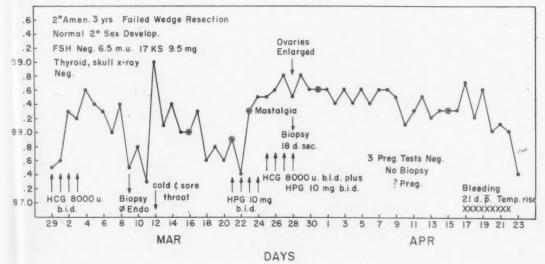


Fig. 3. Basal body temperature graph of Patient J. P. Ovulation probably occurred following administration of HCG/HPG combination.

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Fig. 4. Secretory endometrium D22, obtained from Patient J. W.

Summary and conclusions

Eight amenorrheic women and one normally menstruating woman with endometriosis were given 16 series of injections of human pituitary material consisting of human pituitary extract (HPG) combined in part with chorionic gonadotropin (HCG). One patient responded to the HCG control injections by resuming menstruation and all signs of ovulation and has continued to menstruate and apparently ovulate normally ever since. She therefore was eliminated from the series. In the 7 remaining patients, there were 2 failures of therapy. One was

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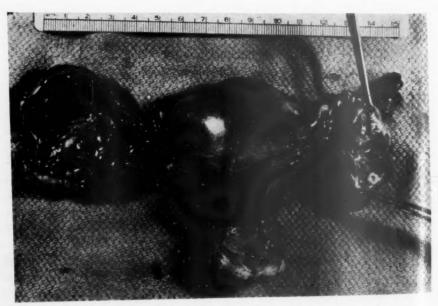


Fig. 5. Gross specimen obtained from normally ovulating control patient who was treated with HCG/HPG series during first half of cycle.

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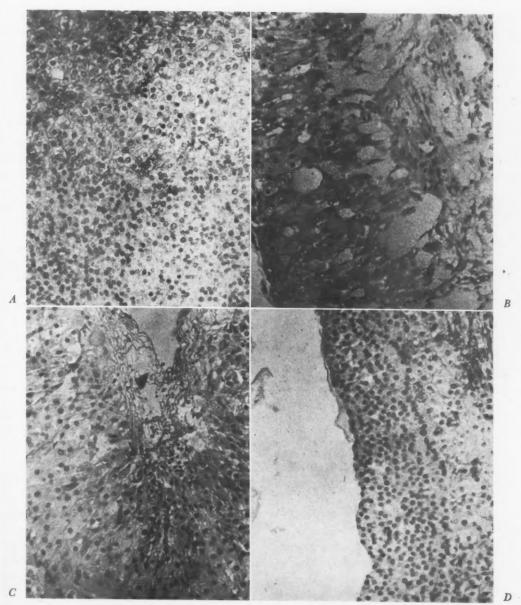


Fig. 6. A-D, Corpora lutea in different stages obtained from ovaries of control patient treated with HCG/HPG combination.

a patient with a diagnosis of congenital adrenal hyperplasia, aged 33, who had at the age of 11 a resection of ovarian tissue and subsequent prolonged treatment with various different steroids-ovarian, testicular, and adrenal. The other patient (thought at one time to have had a Stein-Leventhal syndrome but who had failed to resume menstruation after ovarian wedge resection) re-

sponded to the therapy by uterine bleeding but without evidence of ovulation. She did not, however, receive the full course of therapy which proved to be successful in subsequent cases.* The other patients, amenorrheic for from 3 to 6 years, responded

^{*}Since the presentation of this report, this patient was treated with the full course of therapy, and ovulation occurred.

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to therapy by uterine bleeding from secretory endometrium and had basal body temperature charts characteristic of progestational activity. It was therefore assumed that they had ovulated. One patient who was subjected to culdoscopy appeared to have at least 3 ovulation points on each ovary. One normally menstruating woman with endometriosis was given a course of therapy before the operation which was required for the disease. Both ovaries were enlarged to about three times normal size and had several fresh corpora lutea present as well as cystic enlargement of other follicles.

Conclusions

The findings are similar to the findings when an homologous pituitary preparation was used in the *Macaca mulatta* by van Wagenen and Simpson⁴ and human hormone in a series of over 40 cases now treated by Gemzell.⁶ It would appear that the charac-

teristic response following a full course of treatment is evidence of multiple ovulation. It is impossible to say, of course, whether these ovulations are otherwise normal, but it is possibly of some significance that none of our patients became pregnant and only 2 of Gemzell's patients have become pregnant to date so far as is known. (Both these cases were multiple pregnancies!) Also of considerable significance is the fact that none of the patients who responded to therapy by menstruation and apparent ovulation continued to menstruate or ovulate subsequently.

HPG was provided through the courtesy of Merck & Co., Inc. (Division of Bio-Organic Chemicals, Norman G. Brink, Director), Rahway, New Jersey, in cooperation with Dr. Miriam Simpson, Berkeley, California, who was responsible for the original preparation and assaying of the material. We wish to acknowledge the advice and cooperation of Drs. van Wagenen and Simpson throughout the process of this study.

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Amino acid concentrations in fetal and maternal plasma

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THE fetus, for the most part, synthesizes its own tissue proteins from the essential amino acids which are transported across the placenta from maternal to fetal plasma. It was pointed out by Christensen and Streicher¹ in 1948 that in all species studied the total free amino acid nitrogen concentration is always greater in the fetal than in the maternal plasma, and this led to the concept that the placenta was able to concentrate these materials against a chemical gradient. In all probability, the rate of growth of a fetus is dependent in part upon the degree of such concentration, provided of course that all of the amino acids necessary for complete protein synthesis are increased in appropriate ratios. A knowledge of the nature and of the control of amino acid transport is therefore important for an understanding of intrauterine fetal nutrition and growth.

A simplified schema of amino acid metabolism in pregnancy is shown in Fig. 1. The heavy arrows indicate points of con-

centrative transfer into cells. Each tissue concentrates the amino acids to a different degree, as demonstrated by Noall, Riggs, Walker, and Christensen² who used an unmetabolizable amino acid as their tracer. An essential point brought out by Christensen3 is that these concentrative intracellular transfers are to a large extent under hormonal control. Hydrocortisone, for example, increases amino acid capture by hepatic cells alone, thus increasing the rate of amino acid catabolism, urea formation, and presumably plasma protein synthesis and gluconeogenesis. Estradiol causes a tripling of the amino acid concentration in uterine muscle, and this is followed by myometrial growth. Fetal tissues, trophoblast, tumors, and regenerating tissues take up amino acids more avidly than do adult normal tissues. Thus, increased cellular capture of amino acids is associated with an acceleration of essentially all cellular reactions involving the amino acids.

One method of demonstrating active transport as opposed to diffusion alone is to obtain samples of the extracellular fluid on either side of the placental barrier and determine the relative concentrations of amino acids. If the analytical methods are specific for the free form (as opposed to bound forms) of the solute under study and if in the steady state a chemical gradient can be established, this is presumptive evidence of selective active transport. Crumpler,

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Supported by Grants RG-4702 and RG-6482 from the National Institutes of Health, United States Public Health Service.

Presented at the "Work in Progress" Session of the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960.

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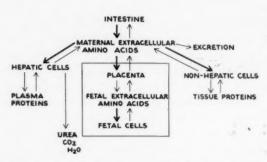


Fig. 1. Amino acid pathways in pregnancy. The heavy arrows indicate points of concentrative transfer.

Dent, and Lindan⁴ have studied the patterns of amino acids by the use of paper chromatography and concluded from the size and intensity of the spots that most amino acids exist in higher concentration on the fetal side. The method, however, is only roughly quantitative and no precise values can be ascribed. The objective of the present report is to present quantitative data with respect to the precise fetal and maternal plasma concentrations of selected essential amino acids.

Methods

Samples of fetal blood were obtained by direct puncture of the umbilical vein as soon as the cord was exposed at the time of elective repeat cesarean section. In two instances, blood was drawn from the maternal antecubital vein simultaneously. Two additional fetal blood samples and 5 additional maternal blood samples were not paired. There were no significant differences in the amino acid concentrations of the paired and unpaired samples, so the data have been pooled for presentation. The heparinized blood was centrifuged and the plasma frozen immediately and stored at -18° C. until the time of analysis.

Proteins were precipitated from diluted plasma with acetic acid at 100° C. After centrifugation the precipitate was extracted with dilute acetic acid. The combined supernate and acetic acid extracts were lyophilized and taken up in a small volume of M/5 hydrochloric acid. An aliquot of the re-

sulting solution was placed upon a column of sulfonated polystyrene cation exchange resin (Amberlite CG-120) for resolution of the individual amino acids. Since the amount of plasma available was limited, the particle size of the resin, the length of the column, and the pH and molarity of the citrate buffers used for elution were selected to permit resolution of both acid and alkaline amino acids from a single application of the sample to one column. The adjustments were made on the basis of principles described by Moore, Spackman, and Stein⁵; Spackman, Moore and Stein⁶; and Hamilton.⁷

All of the amino acids were resolved as single peaks except the pairs threonine-aspartic acid, serine-asparagine, and phenylalanine-tyrosine. Fractions were collected in volumes of 2 ml. by means of an automatic fraction collector. The total amount of amino acid in each tube was obtained by subjecting an aliquot to reaction with nin-hydrin according to the method of Rosen.⁸ Proline was determined by the method of Troll and Lindsley.⁹

The recovery of histidine was less reproducible than that of other amino acids. For this reason, 0.5 μc of histidine C¹⁴ (ring 2) was added to the plasma just before deproteinization. Aliquots of 100 µL of the fractions containing histidine were mixed with 11 ml. of toluene-dioxane-ethanol (5:5:1) containing 0.55 per cent diphenyl oxazole, 0.0028 per cent 1-4-bis (2-[5-phenyl-oxazolyl]) benzene, and 2.75 per cent naphthalene in screw-capped counting vials. The citrate was allowed to settle out and the radioactivity was measured in a Tri-Carb liquid scintillation counter. Analyses for histidine were corrected for any losses detected in the recovery of the tracer.

Result

The mean concentrations of individual amino acids in the samples of fetal and maternal plasma, together with the standard error of the means, are shown in Table I. The amino acids are arranged according to the degree of concentration in fetal blood

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Amino acid	Fetal plasma (\mu mol./liter \display S.E.)	Maternal plasma (µmol./liter ± S.E.)	Ratio (fetal mean maternal mean)		
Lysine	374 ± 11.0	189 ± 11.6	1.98		
Glycine	215 ± 11.1	118 ± 6.1	1.82		
Methionine	37 ± 4.1	21 ± 2.0	1.76		
Threonine and aspartic acid	334 ± 37.1	213 ± 16.8	1.56		
Serine and asparagine	375 ± 38.0	240 ± 30.8	1.56		
Phenylalanine	119 ± 10.2	83 ± 7.1	1.48		
Valine	219 ± 13.1	162 ± 18.6	1.35		
Histidine	151 ± 11.2	112 ± 7.2	1.35		
Alanine	373 ± 36.1	· 281 ± 14.0	1.33		
Isoleucine	62 ± 7.2	50 ± 4.6	1.24		
Leucine	103 ± 8.3	90 ± 7.9	1.14		
Proline	118 ± 7.0	123 ± 13.1	0.96		
Taurine	197 ± 27.0	55 ± 7.2	3.67		
Urea	$2,170 \pm 153$	2.070 ± 183	1.05		

as compared to maternal blood. The fetal to maternal ratios are shown in the third column. In three instances, amino acids are paired because they were not completely resolved from each other by the column chromatography. From the data on maternal blood alone published by Christensen and associates¹⁰ (with which our maternal plasma data are in essential agreement), it may be estimated that aspartic acid constitutes 5 per cent, serine 30 per cent, and tyrosine 40 per cent of their respective pairs.

Proline appears to be the only amino acid which is not higher in the fetal plasma. Taurine, a metabolite of cysteine, is concentrated more than three and one-half times in fetal plasma, presumably because it is produced in the fetus and traverses the placental barrier with difficulty. Urea is also produced by the fetus, but it must diffuse with great ease inasmuch as the chemical gradient is almost insignificant.

Summary

Fetal and maternal plasma samples, obtained at the time of cesarean section, were analyzed by column ion exchange chromatography for individual amino acids. The concentrations of 9 individual and 3 paired amino acids, plus taurine and urea, are compared. Each amino-acid with the exception of proline was found to exist in

higher concentration in the fetal blood. This was found to be true when fetal and maternal blood samples were drawn simultaneously and also when maternal samples were compared to blood samples obtained from the newborn infants of other mothers.

The data are presumed to be evidence favoring an active, mediated transport of the amino acids across the placental barrier. The relationship of these findings to the rate of fetal protein synthesis and to the endocrine control of the cellular uptake of free amino acids is discussed.

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Studies in human myometrium during pregnancy

I. Electrolyte levels-preliminary report

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With the technical assistance of

DANIEL SCHWEID

ALMOST coincidental with the extraction and identification of actomyosin and adenosine triphosphate (ATP) came the recognition of the importance of the concentration of the ions preent when these substances interacted. The contraction of skeletal muscle rests on the triad of actomyosin, ATP, and the proper electrolyte levels. Subsequently, this same sequence was shown to be true, with some modifications, for the proper contraction of uterine muscle.

Initially this observation remained one of laboratory interest only, and the ions were relegated to the role of substrate in test tube experiments. Subsequent tissue analyses, however, indicated the importance of the cation and anion levels in contracting tissues. In uterine muscle, furthermore, it has been demonstrated in the laboratory animal that this ionic concentration is greatly influenced by ovarian steroids.

Myometrial cells, like any other excitable tissue, accumulate potassium inside the cell in preference to sodium, and thus set up an ionic gradient across the cell membrane,

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Aided by United States Public Health Grant RG-7825.

Presented at the "Work in Progress" Session of the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960. since the extracellular fluid is low in potassium and high in sodium. This ionic gradient is responsible for the resting potential observed in most living cells. Measurements of resting potential in the myometrium overlying placental and interplacental sites in rabbits and rats have been made by Goto and Csapo¹ and by Thiersch and associates.² They found a distinct difference in the resting potentials at these two sites during certain phases of the pregnancy. Keeping this difference in mind, we have studied the ionic profile of human myometrium at these two sites and this report deals with the results obtained.

Material and methods

Muscle. Specimens from 9 patients at various stages of pregnancy were obtained from the myometrium overlying the placental and the antiplacental sites, as well as from the lower uterine segment. The clinical episodes included therapeutic abortion, elective repeat cesarean section, and cesarean hysterectomy. The biopsy material was collected in an air-tight bottle and promptly transferred to the laboratory where the tissue was blotted free of superficial blood. The muscle was then cut into small pieces with scissors and duplicate representative samples were transferred to platinum crucibles and weighed. The specimens were dried at 103° C. for 24 hours, then cooled and again weighed, the loss in weight giving

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a measure of the water content. The dry tissue was ashed at 500° C. for 6 hours; the ash was diluted in water and the different analyses were carried out.

Sodium and potassium were determined by flame photometer. Chloride was determined by the Wilson and Ball³ modification of the Van Slyke method. Calcium was analyzed, with calcein used as an indicator, based on the metal chelating property of ethylenediamine tetraacetic acid (EDTA) at above pH 12, where it chelates calcium more easily than magnesium.

No attempt was made for the correction of fat content in the muscle since a previous study revealed that the fat in the uterine muscle is less than 5 per cent and this percentage does not affect electrolyte calculations, according to Manery and Hastings.⁴ Hawkins and Nixon,⁵ in their study of electrolytes in the myometrium, came to a similar conclusion.

To evaluate the validity of our techniques, recovery experiments were carried out and each sample has been analyzed in duplicate along with a standard used as a test unknown. The duplicates were within ±2 mEq. on an average.

Blood specimens were obtained at the time of biopsy. The serum was separated as soon as possible and analyzed for sodium, potassium, chloride, calcium, and water by similar techniques.

Results

Expressed as milliequivalents per 100 grams of tissue in either the wet or the dry weight, interesting differences were demonstrated. In early pregnancy the concentration of sodium from the placental site was lower than that from the antiplacental site, a difference which disappeared as term 'approached. The potassium levels moved in the opposite direction, the placental site potassium being higher than the antiplacental, a difference which disappeared at term and was reversed in the postterm specimens. The differences in calcium levels were less marked but tended to parallel the findings with respect to sodium. Early

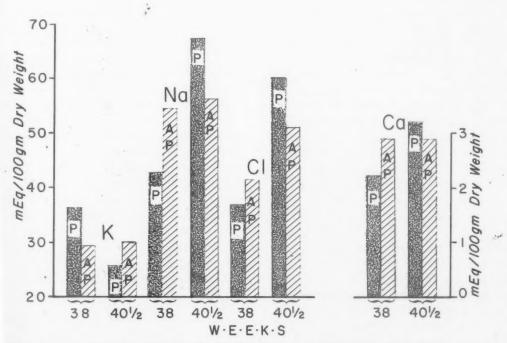


Fig. 1. Total tissue electrolytes at placental and antiplacental sites in 2 typical patients, one at 38 weeks and one at 40-plus weeks. It can be seen that the differences between the placental and antiplacental electrolyte levels shift during this stage of pregnancy.

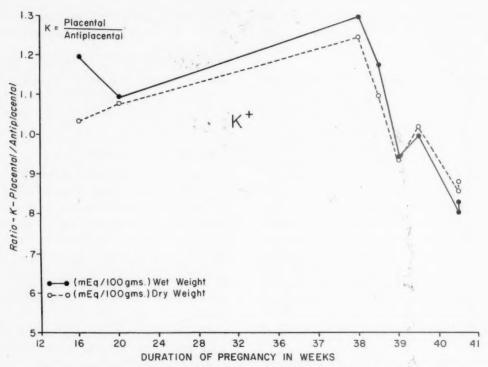


Fig. 2. The tissue potassium from the placental site divided by the potassium level from the antiplacental site (one curve for dry weight and one for wet weight determinations). As pregnancy progresses this ratio rises then drops below 1 in the last few weeks.

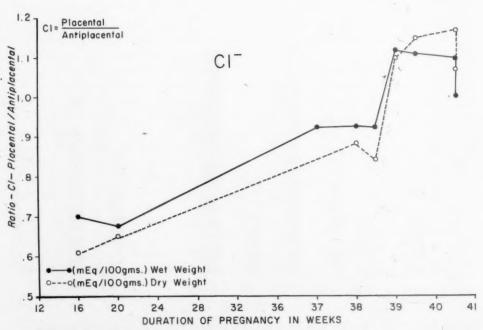


Fig. 3. Tissue chloride levels recorded by the ratio of the placental to the antiplacental sites. This ratio shifts in a manner which is almost the reverse of the potassium levels seen in Fig. 2.

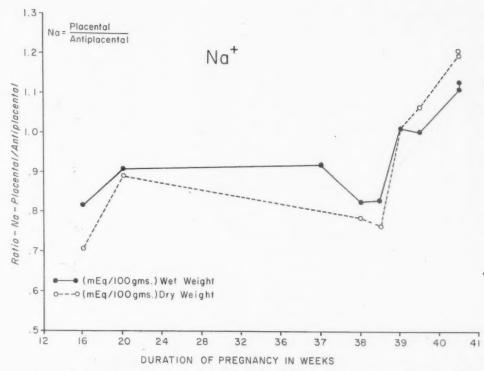


Fig. 4. The placental-antiplacental ratio for sodium charted by the week of pregnancy.

in pregnancy the chloride concentration was lower at the placental than at the antiplacental site. These chloride differences were most marked with respect to the dry weights and gradually shifted until the placental site had the higher level at term. While reproduction of all the data from these multiple analyses is not feasible, Fig. 1 illustrates 2 typical cases.

With these data, the intracellular cation levels were calculated by means of the method of Hastings and Eichelberger.6 This method is based on the assumption that all chloride is extracellular; but, with differing chloride levels both at different parts of the uterus and in different stages of pregnancy, this technique yielded inconsistent and often bizarre results. As is the case with smooth muscle, the basic assumption of this calculation is open to question, and one needs to assume the presence of some chloride within the cell.

These differences between the ionic level at the placental versus the antiplacental site can also be illustrated by calculating the ratio (placental/antiplacental) and graphing this by the week of pregnancy. Fig. 2 shows this ratio for potassium, indicating the rising level of this ion at the placental site during pregnancy with a sharp reversal in the term and postterm specimens.

The higher levels of potassium in the placental site before term can be substantiated from a case of placenta previa in our series. In this case the implantation of the placenta in the lower uterine segment was associated with a level of 5.15 mEq. per 100 grams of wet weight tissue, in contrast to an average level in this portion of the uterus of 4.02 mEq. per 100 grams wet weight tissue.

Fig. 3 shows the trend for the chloride ion. It can be seen that the chloride tends to be lower at the placental site when the potassium concentration is high and vice versa. This ratio for the sodium ions is illustrated in Fig. 4. The sodium is lower at the placental in comparison to the antiplacental site during the first trimester. This trend is maintained up to 39 weeks

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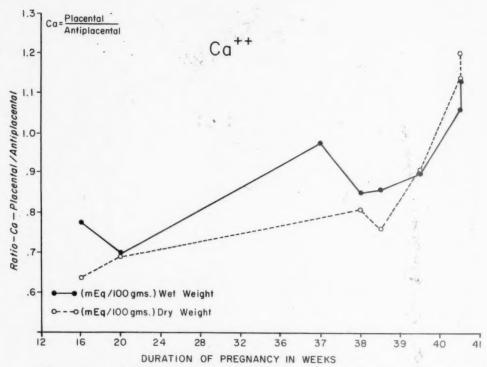


Fig. 5. The ratio of placental site level to antiplacental site level for calcium roughly approximates that found for sodium.

of gestation, after which the sodium at the placental site increases. The calcium ion follows this same trend. (Fig. 5).

The total tissue water content at these two sites and the trend for all the ions together is shown in Fig. 6. In contrast to the electrolyte profile, the total water content does not vary in these two sites.

As previously indicated, the myometrium of the lower uterine segment presents the lowest potassium level except when the placenta is overlying it. Whether from the placental or antiplacental area, the myometrium of the upper uterine segment had lower levels of sodium, chloride, and calcium than did the lower segment. The water content, however, was found to be the same in both upper and lower uterine segments.

Comment

This is the first study with which we are acquainted dealing with the tissue electrolytes in the human uterus comparing the placental versus antiplacental sites. It is a preliminary study and needs more data as well as confirmation by others.

Our finding of a higher tissue potassium content in the myometrium overlying the placenta suggests a higher resting potential in this area since the resting potential is dependent mainly on the potassium gradient. Such a higher resting potential at the placental versus the antiplacental site has been observed in rabbits by Goto and Csapo¹ and in rats by Thiersch and co-workers,² and we are currently engaged in obtaining such measurements in human myometrium.

While precise calculations cannot be made of intracellular levels, as previously indicated, the finding of a high total tissue potassium strongly suggests a high intracellular potassium level as long as the blood potassium level remains constant. The likelihood of this being the case is indicated by our data on chlorides which reveal a lowered chloride level at the placental compared to the antiplacental site. In general, of course, the chloride distribution is entirely passive and

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the two major forces which control its gradient across a cell membrane are the electrical gradient and the cation concentration. The chloride is low intracellularly because the electrical gradient forces chloride out until equilibrium is reached. A higher intracellular potassium level increasing the resting potential would move chloride out, resulting in the lowered chloride levels observed in our samples taken from the placental site.

The assumption that increases in intracellular potassium levels in the myometrium (and hence increases in the resting potential) are synonymous with increased local progesterone activity is an assumption currently made by most workers. It is based on the observation that in the experimental animal progesterone treatment raises the resting potential above that found in an estrogendominated uterus. Likewise, Daniel7 has reported changes in tissue electrolyte levels in the uterus of the estrogen-primed cat after

treatment with progesterone—the total potassium rising and the sodium and chloride falling in response to the administration of progesterone. Accordingly, the assumption is suggested that this difference in human myometrium represents a local effect of placentally produced progesterone acting directly on the adjacent myometrial cells.

The lowered levels of total tissue calcium at the placental sites when the potassium concentration has been found to be higher is difficult to explain at present. Even though the role of total tissue calcium is not entirely clear, Houssay⁸ is of the opinion that calcium in some way antagonizes the action of potassium in the muscle contraction. Furthermore, Csapo⁹ is of the opinion that a labile fraction of the muscle calcium is more firmly bound under progesterone domination than under estrogen alone. Our present experiments concerning the estimation of diffusible and nondiffusible calcium at the placental and antiplacental sites may throw

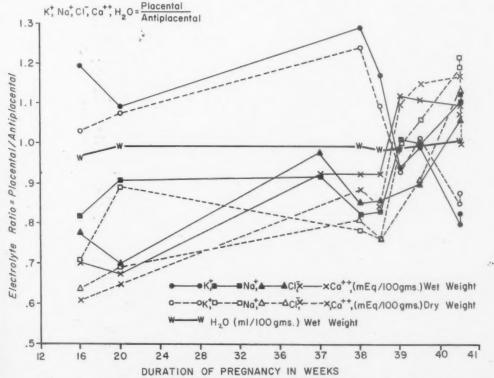


Fig. 6. Composite curves for the electrolytes shown in Figs. 2 to 5. This graph also illustrates the values found for tissue water, which remained reasonably constant throughout pregnancy.

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The reversal at and post term of the ionic profile in the uterine muscle at these two sites could be a matter for great speculation. The only thing one can say is that some change in the ionic profile of the myometrium does occur at the onset of labor.

It would be helpful if we had intracellular values for these ions instead of total tissue concentrations for the calculation of theoretical resting potential. We have attempted to use the in vitro chloride and thiocyanate spaces for such determinations without complete success. Our values for extracellular space based on these two methods are the same and range around 50 to 60 per cent of the total tissue volume. Daniel7 has also reported a larger extracellular space in the uterine muscle in comparison to the striated one. It would seem from the above data that a substantial portion of the chloride estimated as total tissue concentration is inside the cell and that the uterine smooth muscle membrane is permeable to the thiocyanate. The use of radioactive techniques for the in vitro estimation of the extracellular

space may provide the answer in the uterinmuscle.

Summary

Tissue electrolyte levels were determined in human myometrium, and the placental site compared with the antiplacental. Differences in the sodium, potassium, chloride, and calcium contents were noted between these two areas, a difference with respect to each ion which shifted with the duration of pregnancy.

Addendum. Since this paper was prepared for publication, E. E. Daniel has reported a similar study on the myometrium of pregnant cats (Am. J. Obst. & Gynec. 80: 229, 1960). His figures substantiate the findings in the human being by showing an excess of potassium in the placental compared to the nonplacental myometrium, an excess which disappears as the fetus becomes larger. His findings differ from those presented here by indicating that in the laboratory animal the water content of the myometrium over the placenta is lower than that from nonplacental areas, a difference which also disappears as term approaches.

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Pregnancy toxemia and sodium chloride

Preliminary report

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THE belief that sodium chloride is intimately associated with the etiology of preeclampsia is ingrained in the minds of most physicians. It is so firmly intrenched that generally the first thought regarding treatment of the disease is sharp reduction in the dietary intake of salt. It is even believed by some that restriction of sodium chloride in normal pregnancy is prophylactic against development of toxemia of pregnancy. There is every reason to doubt these beliefs. It is true that excessive quantities of parenterally injected sodium chloride will produce edema, hypertension, and coma in animals and in humans. The quantities necessary to do this bear no resemblance to those normally ingested even by people who eat excessive amounts. It is true that convulsions have been produced in dogs with water alone, by forced ingestion through a stomach tube. It is also true that convulsions simulating those of eclampsia can be produced by many chemicals and occur with many diseases. The fact that any or all of these things are true has little, if anything, to do with the etiology of pre-eclampsia-eclampsia.

From long years of clinical observation it

would seem that edema during preeclampsia may arise from causes other than salt retention. Otherwise, why do not an appreciable number of the women who experience the benign swelling of the ankles and lower legs of early pregnancy develop pre-eclampsia? Certainly, this edema is largely due to salt retention, is generally successfully treated by sodium restriction, postural drainage, and increased fluid intake, and has no ominous prognostic importance.

On the other hand, when acute vasospastic toxemia develops in the second semester, or third trimester, there is frequently no significant degree of edema. Why, therefore, have we concentrated attention on salt retention and assumed it is etiologically significant? Consider vulvar edema, occasionally seen in fantastic degree with preeclampsia. It is extremely difficult to explain such a localized phenomenon on the basis of salt retention. The acute, vasospastic toxemia of human pregnancy is, however, entirely capable of producing intense, localized phenomena. Although the arteriolar spasm of pre-eclampsia is generalized throughout the body, the spasmodic intensity varies with anatomic location. Chambers and Zweifach⁴ studied the capillary bed and the transport of blood through it from arteriole to venule. From perusal of their publications it seems that arteriolar spasm might affect the normal mechanisms known as "vasomotion" to the extent necessary to

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Presented at the "Work in Progress" Session of the Seventy-first Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Sept. 8-10, 1960.

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produce accumulations of extracellular fluid. In other words, localized accumulations of fluid may be caused by mechanisms other than salt retention. In patients suffering from toxemia of pregnancy, more than one mechanism resulting in fluid storage may be operative. This would explain some of the marked variations in degree of edema seen with preeclampsia. Probably salt retention edema is coincidental and concurrent with edema caused by pre-eclampsia. It may be that salt retention is the result, rather than the cause of pre-eclampsia.

Six years ago, acting upon these beliefs, we gave a standard diet containing normal quantities of salt to all toxemic patients at Parkland Hospital in Dallas, during a period of 6 months. There was no discernible alteration of the clinical course of the toxemia. No further work was done until the present study began.

Patients and materials

Beginning in February, 1959, consecutive and alternating patients with acute vaso-spastic toxemia of pregnancy (pre-eclampsia) were given either a high salt or a low salt diet. The average quantity of salt in the high salt diet was 10.0 to 11.5 Gm. of sodium chloride, or 6 to 7 Gm. of sodium element. The low salt diet contained 0.9 to 1.7 Gm. of sodium chloride, or 0.5 to 1.0 Gm. of sodium element. The patients were carefully checked to ensure that sodium in other forms, for example, bicarbonate, was withheld. Each day all patients were weighed and the

Table I. Patient data

,	Low salt diet	High salt diet	
Mild toxemia	16	10	
Severe toxemia	8	14	
Twins	3 sets	2 sets	
Hospital stay (days)			
Range	3-31	3-20	
Average	9.3	9.5	
Deaths			
Maternal	1*	-	
Fetal, stillbirth	2	2	
Neonatal	1	1	

[&]quot;Died post partum of severe bronchial asthma.

Table II. Average daily weight change per patient (grams)

Low salt diet		High salt die		
Loss	16 (19 patients)	16 (16 patients		
Gain	82 (2 patients)	21 (6 patient		

Table III. Average values of blood and urinary sodium (mEq. per liter)

	Low salt diet		High salt diet		
	Blood	Urine	Blood	Urine	
Range	125-144	33-140	135-142	34-140	
Ante partum	139.7	67.1	139.8	60.8	
Post partum	139.4	68.8	139.9	60.9	
Total	139.6	67.4	139.8	60.8	

24 hour intake and output measured and recorded. The blood pressure was recorded, and blood and urinary sodium levels were estimated with a flame photometer. In addition, the patients were carefully followed clinically. The retinas were examined with an ophthalmoscope at least once, and usually more often. Other clinical and laboratory tests were performed as indicated. This clinical study continued for 11 months, until January, 1960, and included 48 patients with acute pre-eclampsia. In so far as clinical acumen permitted, patients with chronic hypertensive vascular disease only were excluded from the study. Patients with one or more blood pressure recordings of 160/100 or higher were classified as having severe disease. Others were considered to have the disease in a mild form.

Data on patients are included in Table I. The two groups in general are comparable. In passing it is interesting to note that 5 of these 48 toxemic women gave birth to twins, indicating once again that multiple pregnancy and toxemia are somehow associated.

Results

Basically, no differences were noted between the two series. The time necessary for recovery to normotensive levels, disuppearance of arteriolar spasm, proteinuia, and the changes in patients' body weights were similar.

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Table II shows the weight in grams, gained or lost. There were no significant differences. Table III depicts the average values of blood and urinary sodium in milliequivalents per liter. In the low salt group the urinary sodium levels are slightly higher than they are in the high salt group. Otherwise the two groups are similar.

Comment

A clinical experiment was designed to answer the question: Do dietary differences in salt ingestion alter the course of acute, vasospastic toxemia of pregnancy? In our small series of 48 consecutive patients, alternating with regard to salt ingestion, there were no significant differences. In other words, under the terms of the experiment as outlined, the clinical course of acute vasospastic toxemia remained unaltered.

Dieckmann¹ said in his book, The Toxemias of Pregnancy, "It was surprising to note that of the patients who had been referred to the toxemia clinic because of hypertension, edema, proteinuria, or too rapid weight gain, 63 per cent showed no edema or no change in the degree of edema after the administration of sodium chloride or sodium bicarbonate. . . . We were still more surprised when 12 per cent of the patients who had had edema showed a decrease after the administration of sodium salts. . . . These were all presumably abnormal patients that had been referred to the toxemia clinic, and yet in only 25 per cent was there a presumable association with sodium salts."

Robinson² in 1958 reported that she started giving salt to pregnant women in order to lessen leg cramps. After giving salt to a large number of women, she ascertained there was no increase in incidence of toxemia. Then she started giving salt to toxemic women. In all, 2,077 women were investigated; 1,039 took added salt and 1,038 decreased salt intake. The incidence of toxemia, edema, perinatal death, and antepartum hemorrhage was decreased. Of the group taking extra salt, 17 women had transitory symptoms of toxemia. In addition to the above series, 20 women with early toxemia were treated with extra salt. All of them improved and the larger the dosage of salt taken, the quicker and more complete was the recovery. Robinson concluded that "extra salt in the diet seems to be essential to the health of a pregnant woman, her foetus, and the placenta." As noted above, this did not begin as a controlled experiment directed at toxemia.

The present study is small in numbers. No claim whatsoever is made from the results, except that under the circumstances described there were no significant differences between the two groups. It is presented with the hope that it will stimulate others to ask the question, "Is sodium chloride etiologically associated with pre-eclampsia?"

Summary

Forty-eight consecutively admitted patients with acute, vasospastic toxemia of pregnancy were alternately given diets with 10.0 to 11.5 Gm. of sodium chloride and 0.9 to 1.7 Gm. of sodium chloride daily.

There was no discernible effect on the clinical course of the toxemia.

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Discussion

DR. RUSSELL R. DE ALVAREZ, Seattle, Washingion. By definition, edema is characterized as an expansion of the extracellular space pre-

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dominantly by sodium chloride in water. The retention of sodium plays a significant role in all forms of edema, whether it be associated with cardiac failure, renal insufficiency, hepatic cirrhosis, or pre-eclamptic toxemia. Edema, usually one of the typical signs of pre-eclampsiaeclampsia, does not occur in every instance of the toxemic process. Whether toxemia of pregnancy is due to the edema and the mechanisms responsible for edema formation or whether the edema is a direct result of the toxemic process is not presently known. What is known, however, is that an increase in extracellular fluid volume occurs during normal pregnancy. It is also known that when the extracellular fluid volume is increased it is associated with sodium retention. In correcting this expanded space, through careful water and sodium balance, initial plasma isosmolarity occurs provided sodium depletion is not permitted to occur.

In an attempt to clarify possible interrelationships between electrolyte balance and some of the increases in weight said to be due to water retention during pregnancy, we carried out balance studies on a patient with pre-eclampsia, first on a low sodium diet containing 800 mg. of sodium (34.8 mEq.) for 4 days, during the antepartum period. This was continued for 3 days post partum following which the same diet was augmented by the administration of 15 Gm. of sodium chloride (256 mEq. of sodium). The positive balance of sodium increased sharply to very high levels. The mean retention was 70.9 per cent of the sodium intake as compared to 51 per cent on the low sodium diet alone. The urine sodium output was slow to respond to the administration of the increased sodium intake, increasing only from 5 mEq. while on the low salt diet to 12 mEq. on the first day of the high sodium. However, on the third day of high salt, the urinary excretion rose to 151 mEq., with its cumulative effect continuing to a high of 295 mEq. even after the ingestion of high sodium was discontinued. Changes in serum sodium seemed to be relatively independent of changes in urine sodium despite the augmentation of sodium chloride intake. The only thing which we could conclude was that the patient on a low sodium intake prior to delivery is an excellent candidate for the development of hyponatremia and immediate puerperal shock with associated adrenocortical failure.

In the patient with pre-eclampsia-eclampsia the retention of sodium and thus of water may be produced by several factors, any one of which may initiate a cycle or a series of cyclic events. In severe pre-eclampsia glomerular filtration and renal blood flow are markedly reduced, enhancing the tubular reabsorption of sodium. While we have noted no increase in plasma sodium concentration as a result of this increased realsorptive mechanism, it is known that an increase in the sodium space occurs. This could be responsible for stimulation of the supraopticohypophyseal system to enhance the production of ADH which, in turn, increases reabsorption of water at a practically simultaneous rate to explain the maintenance of normal osmolarity. Under these circumstances extracellular fluid volume is increased bringing about two mechanisms to reduce enhancement of the cycle. The first of these is inhibition of ADH secretion and the second, an attempt to inhibit the adrenocortical output of aldosterone.

The "high" sodium diet of 15.0 to 17.0 Gm. of sodium chloride per day used by Mengert in his study is satisfactory but only slightly exceeds the sodium chloride content of some average American diets (Table I). His high salt diet is well above the range of the average salt-free diet. It contains 6.0 to 7.0 Gm. of sodium (257 to 304 mEq.), cooked with an amount of sodium chloride necessary to season but with no salt added after cooking.

Dr. Mengert's low salt diet (500 to 1,000 mg. of sodium) is indeed a low sodium diet, and conforms to the average salt-free diet. Such a low sodium diet requires a protein content considerably below the level necessary for normal or toxemic pregnancy. A definite relationship exists between the protein content in the diet and a degree of sodium restriction attainable. With Dr. Mengert's low sodium chloride diet it is possible to supply adequate calories but often at some sacrifice to the qualitative factors in dietary protein.

Table I. Dietary sodium content

Diet	NaCl (Gm.)	Na (Gm.)	Na (mEq.)	
Average				
American	6.0-15.0	2.4 -5.9	103-257	
Mengert's high				
salt	15.0-17.0	6.0 -7.0	257-304	
Average salt				
free*	2.0- 4.0	0.78-1.57	34- 68	
Neutral ash salt				
free*	2.0	0.80	35	
Kempner's rice	0.390	0.15	6	
Mengert's low				
salt	1.2- 2.4	0.5 -1.0	2213	

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03-257 57-304 34- 68 35 6 In the same connection, but on the other hand, the high protein diet forms an important part of the prenatal care of the normal pregnant patient. Thus, it would seem logical, on the basis of the increased sodium content of the high protein diet, to advise some degree of sodium restriction throughout pregnancy since the amount of sodium already contained in this normal diet approximates 2.5 Gm. (105 mEq.) daily.

Dr. Mengert's data in his Table III show an increase in urinary sodium concentration. This fact does not represent any evidence of the total urinary sodium excretion. The total 24 hour urinary output would have to be known in order to determine the total 24 hour urinary sodium excretion. Other considerations also come into play such as information as to whether the patients were hospitalized, whether they were receiving diuretics, whether they were on bed rest alone, water balance, and the duration of the increased sodium intake. Dealing with concentration, it is known that the horizontal position alone increases pressure in the receptors of the carotid body; this would tend to halt aldosterone secretion and therefore enhance sodium ion excretion regardless of quantity ingested.

In specific instances of severe toxemia of pregnancy, we have been able to resolve completely all objective evidences; of severe pre-eclampsia utilizing our approach to therapy. After complete control and return to clinically "normal," without evidences of pre-eclampsia, we undertook to "reverse" the process by attempting to reproduce the clinical evidences of pre-eclampsia. Sodium chloride in 25 Gm. doses was administered daily with the occurrence of the so-

called characteristic findings of pre-eclampsia in the following order: weight gain, demonstrable edema, elevation of the blood pressure, return of proteinuria, and, in one instance, very markedly hyperactive reflexes with irritability but without the production of convulsions.

Dr. Mengert has presented his material with the hope to stimulate investigation to determine whether sodium chloride produces pre-eclampsia. I believe the research must include careful controls and should be carried out under strict metabolic balance, including nitrogen balance. Since the etiology of toxemia of pregnancy is as yet unknown, except for the presence or the influence of pregnancy, despite the tremendous amount of investigation in search of its cause, one could not agree more fully with his conclusion that salt alone is not THE cause of preeclampsia. I do believe, however, that excessive amounts of the sodium ion will reproduce the pre-eclamptic picture once it has been present where the influence necessary for production exists. I believe, therefore, that we must conclude that sodium chloride contributes to the cause of pre-eclampsia, aggravates already existing pre-eclampsia, and even contributes largely to one of the most frequent causes of death in pre-eclampsia, pulmonary edema.

DR. MENGERT (Closing). This was a clinical study which made no pretense of being a metabolic study. The patients were allowed bathroom privileges. No diuretics were given and the diets were continued for the duration of the hospital stay.

CURRENT OPINION

Clinical problems

Premenstrual tension

Case presentation

Mrs. A. C., aged 46 years, complained of nervousness, irritability and extreme tenderness of the breast for the 10 days preceding each menstruation. These symptoms had been present for approximately 15 years but had been becoming more severe and troublesome in the preceding 3 years. On occasion they were accompanied by moderately severe headaches. On direct questioning the patient stated that she gained 4 to 6 pounds in weight shortly before each menstruation and that this weight was lost during the menstrual period.

Physical examination. The results of all physical, pelvic, and laboratory examinations were normal.

Problem: Would you discuss this medical condition and the management of this patient.

Consultation

S. J. Behrman, M.D. Ann Arbor, Michigan

Department of Obstetrics and Gynecology, University of Michigan Medical School

The problem presented here is neither a simple nor a well-understood one although it occurs with far more frequency than many suspect and presents a symptom-complex too often neglected or lumped into some other diagnosis. Yet, to the patient, the cyclic recurrent symptoms of nervousness, irritability, depression, insomnia, etc., may be so disturbing as to have serious consequences; so much so that she may develop a real dread of insanity. In fact, studies of

female inmates in mental hospitals reveal that better than 60 per cent of suicides were attempted just premenstrually.

The clue to the diagnosis in this case is the weight gain of 4 to 6 pounds occurring premenstrually, which, incidentally, is quite average for this condition. This, in addition to the other symptoms occuring repetitively in cyclic fashion 3 to 10 days prior to the onset of menses, gives us the diagnosis of the premenstrual tension syndrome. The symptoms given are typical; others not infrequently found are a feeling of abdominal "bloating," tremors, fainting, crying spells, anxiety, insomnia, and moods of depression that on occasion can be extreme. This diversity of symptoms and the indeterminate etiology necessitates the individualization of treatment to be discussed.

The premenstrual tension syndrome complex reveals a combination of physical and psychological disturbances of which (1) excess fluid retention, (2) hormone imbalances, and (3) emotional tension and disturbances are the main features. Although the precise etiology is not known, current opinion attempts to explain the syndrome with some of the following theories:

1. An imbalance of the estrogen and progesterone ratio. The relative increase in estrogen is held responsible for sodium retention resulting in an increased intracellular fluid accumulation and edema. The edema in turn gives the "bloating" feeling, breast tenderness, and cerebral edema with irritability and headaches. The total fluid

accumulated is responsible for the weight gain. The estrogen may also cause proliferation of the lining of the breast ducts with resultant tenderness. Concomitant with these hormonal imbalances, one may find hypoglycemia resulting in the symptoms of faintness, weakness, tremors, and nervousness.

2. Overproduction of the antidiuretic hormone excretion has also been implicated as a potential causative factor, as has endogenous hormonal allergy.

3. Another possible etiological factor that bears remembering is hyperadrenocortical activity with increased production of aldosterone. In the rare case of primary aldosteronism, selective renal tubular reabsorption of sodium is favored with concomitant loss of potassium. This results in fluid collection in the intracellular spaces with a picture of premenstrual tension on the one hand, and lassitude and weakness resulting from potassium loss on the other. However, the weakness here is somewhat out of proportion to what one usually sees in the usual case of premenstrual tension. The theory of estrogen-progesterone ratio imbalance seems to be the most commonly accepted today.

Needless to say, part of the treatment is firmly establishing the diagnosis by careful history with judicious questioning. From here on, a major part of the treatment is giving the patient an opportunity to talk the problem out while you are listening. The patient is not a crank but has a definite problem and comes seeking solace and help. The mere act of listening (allowing her to taik!) is therapeutic in itself and also permits a shrewd observer to pick up a real "gold-bricker" and perhaps the missed diagnosis of some other disease. The heavy overlay of psychological disturbances as well as physical infirmity indicates the importance of bolstering the morale of the patient as part of your treatment. From here on, the management is:

A. The control of water retention. Moderate sodium restriction for the second half of the cycle together with a suitable diuretic will prevent the weight gain and often give

dramatic results. Some of the more frequently used diuretics today are hydrochlorothiazide and benzothiadiazine given for 3 successive days and off for 3 days successively for the 10 days prior to the expected onset of the menses. It is well to bear in mind that these diuretics, if used for too long a period of time, may cause loss of potassium and consequent secondary aldosteronuria. This can be combated with aldosterone, which apparently prevents the selective loss of potassium through the renal tubules.

B. Attention can now be focused upon the presence of any emotional instability. If depression and weepiness or crying jags are the major disturbances, small doses of dextro-amphetamine and amobarbital will help; if excessive nervousness and tenseness are the outstanding features, then small doses of one of the many tranquilizers can be used. However, more important in the management is taking the time to listen to the patient's problems, to explain the nature of this condition to her as best you can, and above all reassure her as to its frequency and relative ease of control, that she is not likely to "go insane," and that it does not suggest serious psychiatric disturbances. This cannot be stressed too strongly.

C. Finally, what about the use of hormones? Estrogen obviously has no role here. Androgens, by virtue of the nitrogen retention and anabolic effects, may help because of the concomitant feeling of well-being but should preferably not be used in view of the ever present danger of masculinization. Progesterone has been suggested in this regard by some but to date there is insufficient evidence to justify its use. It may be of-interest to note that preparations are available containing D-amphetamine, a diuretic and progesterone in combination. Although this "shotgun" tablet may be ideal, it does lack the versatility of individual drugs and individualizing treatment.

Finally, in this particular case, it will be noted that the patient is 46 years of age and soon approaching the menopause, yet

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case is curring s quite ddition titively to the osis of the not inominal spells, cression this diminate tion of

e comcal and (1) exclances, chances precise ion ath some

ease in um reracellua. The feeling, na with for the last 3 years symptoms have become more severe. This is not too surprising as it would seem logical that with the greater frequency of anovulatory cycles at this age period there could be a relatively higher ratio of estrogen and hence fluid retention, etc. Reassurance that the severity of the symptoms will decrease markedly with the menopause, which is imminent, is then also indicated. It is obvious that a surgical approach, e.g., hysterectomy, here just because the patient is approaching the menopause is completely contraindicated.

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Since it was first described in 1938 by Frank, the syndrome of premenstrual tension has emerged as a definite disease entity.

The above patient complains of characteristic symptoms of this condition although as a general rule premenstrual tension occurs in younger women in the thirties and early forties.

This abnormality is presumably due to alterations in ovarian steroid metabolism resulting in concentration of either estrogen or progesterone, or possibly metabolic products thereof, during the latter part of the menstrual cycle. This is in a fashion similar to the action of aldosterone in producing salt retention which results in fluid accumulation in all of the body tissues. Because of this a patient may develop a premenstrual weight gain of 5 or more pounds. Keeping a careful weight chart is one satisfactory way of identifying this disease entity.

The cause of the neurological symptoms of irritability, tension, and depression is thought to be cerebral edema as well as possible edema of other nerve tissues.

If this concept of the etiology of the disease and the source of psychic and neurological symptoms is correct the obvious appropriate therapy is simple but not excessive dehydration, and, indeed, this does have a most satisfactory effect. Reasonable salt restriction together with the administration of a diuretic during the latter half of the menstrual cycle usually results in relief of symptoms. Chlorothiazide in amounts of 250 mg. per day started about 14 days premenstrually, taken for 5 days, followed by a pause for 2 days, and then repeated provides adequate diuresis.

Various types of hormone therapy have been suggested, including testosterone and progesterone, presumably on the basis that the apparent steroid metabolism abnormality may be due to unopposed estrogen activity. This has not been particularly satisfactory, however, and it is expensive and may have undesirable side effects.

It is probable that the increased nervous irritability produced by this condition is noticed more by a patient of an emotionally labile temperament or one who is existing in an underlying state of conflict and tension anyhow. The added nervous irritability may bring these symptoms more sharply into focus in one indvidual whereas in another in a more stable environment this added neurological insult may not be noticed. This may also be one of the reasons why some women notice tension premenstrually during some cycles and not during others, depending a little on what their environmental status is. Certainly a careful explanation of this condition relieves many women of great anxiety and apprehension concerning thoughts of neurasthenia and psychoneurosis.

Editor's comment

This patient was relieved adequately by reduction in fluid and salt intake and the administration of chlorothiazide, 500 mg. daily, during the last half of the menstrual cycle. However, some patients derive meager relief with such therapy and, as both Consultants have indicated, this is probably due to a coexisting strong emotional component.

From a practical standpoint, many pations, while obtaining relief with the described therapy, find it so difficult, impractical, and unpleasant to restrict the fluid and salt intake for 10 to 14 days each month that they prefer the headaches and other symptoms to the medical management. Salt substitutes may remove some of the objections. As mentioned by one of the Consultants, the use of a specific aldosterone

blocking agent might prevent excessive potassium loss occurring with prolonged use of diuretic medicaments.

The development of emotional stability seems a more logical and reasonable approach to this problem.

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Intrauterine death at thirty-fourth week

Case presentation

Patient N. B., aged 26 years, gravida iii, para iii, blood type O, Rh negative (father type A, Rh positive, homozygous), gave the following obstetric history: the first pregnancy was complicated by toxemia, ended with normal term delivery of a normal Rhpositive infant weighing 4 pounds, 9 ounces; the second pregnancy was accompanied by rising titers:

Weeks gestation	Saline	Albumin	Coombs	Trypsin
36	0	1:64	1:64	1:64
37	0	1:128	1:128	1:128
38	0	1:256	1:256	1:256

It was terminated by cesarean section at 38 weeks for the indication of rising titers.

Examination of the living infant revealed: weight, 5 pounds, 8 ounces; normal size liver and spleen; Rh positive; Coombs positive; bilirubin level 5.3 mg. per cent; hemoglobin level 19 Gm. per 100 c.c., and erythrocyte count 4.8 million. Two exchange transfusions were given at 2 and 14 hours after birth. The infant did well.

In the third and present pregnancy the patient had noted cessation of fetal movements during the thirty-fourth week and at the end of that week of gestation her obstetrician made the diagnosis of fetal death. The obstetric conditions were: previous cesarean section, Rh-negative mother with history of one erythroblastotic infant, present gestation at end of thirty-fourth week, fetal death; elevation of titer; not in labor; normal fibrinogen level; cephalic presentation, head at minus-3 station; cervix long and 1.5 cm. dilated.

Problem: Would you discuss the management of this patient.

Consultation

William F. Mengert, M.D. Chicago, Illinois
Professor and Head,
College of Medicine,
University of Illinois

This young woman, pregnant for the third time, is said to have intrauterine fetal death at the thirty-fourth week, presumably from erythroblastosis. From the wording of the case presentation it would seem that whoever wrote it believes all of this patient's obstetric difficulties during the second and third pregnancies were due to erythroblastosis. On the contrary, evidence to support this point of view is meager.

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We are being asked to discuss the management of this patient in her third pregnancy. Such discussion would seem to center around: (1) Is the child dead? (2) If so, should pregnancy be terminated? (3) What is the future reproductive potential of this patient?

1. Is the child dead? No evidence whatever is given for intrauterine fetal death other than the absence of fetal movements and the bald statement that "her obstetrician made the diagnosis of fetal death." No mention is made of Spalding's sign, of angulation of the backbone, or of air in the chambers of the fetal heart. We are left with the idea that fetal death was diagnosed because the fetal heart could no longer be heard. This is certainly insufficient evidence and no positive move should be made on this basis alone.

2. The question of termination of pregnancy revolves around whether or not the child is really dead. If so, it represents biologic waste, and I personally would terminate the pregnancy. Obstetricians are sharply divided into two schools of thought

regarding interruption of pregnancy with abvious biologic waste. Many would do nothing until forced to do so by declining blood levels of fibrinogen. They argue that there is no mandate to do anything. The other school of thought, more often held by academicians than by men whose basic living comes from private practice, insist that when pregnancy wastage is certain, the sooner the wastage is removed the more quickly the woman can regain reproductive efficiency.

Therefore I would terminate pregnancy. I would rupture the membranes and give an infusion of posterior pituitary extract, starting with an extremely small dose and gradually building up until uterine contractions ensue. I consider it dangerous to let an infusion for induction go longer than 3 hours. If it has not achieved its objective by this time, stop and try again the next day. If the first infusion does not stimulate labor after rupture of the membranes, I would repeat the oxytocic the following morning. If the second one does not work, I would perform abdominal hysterotomy.

3. Discussion of the future reproductive potential of this patient involves an understanding of whether or not the second and third children were really erythroblastotic.

We are told the husband is homozygous. Is he? No genotype is given. What evidence is there except that the first and second children are Rh positive?

During the second gestation, titers are said to have risen. On the other hand, the three different laboratory methods support each other so beautifully, one is automatically suspicious of error because of the preciseness of results of tests which commonly are not precise. Moreover, it is well recognized by competent authority that rising titers do not necessarily mean progressive hemolytic disease.

The living infant was essentially normal, although the Coombs test was positive. The bilirubin level (if it was taken during the first day of life) is essentially within normal limits. The hemoglobin of 19 Gm. per 100 c.c. would not indicate anemia, although

the erythrocyte count does not quite match the hemoglobin. I would be suspicious that the two exchange transfusions given at 2 and 14 hours were unnecessary and that the infant did well in spite of them. Sentiment is developing in some circles toward doing exchange transfusions only when the bilirubin level is high. A bilirubin level of 5.3 mg. per cent is well within normal limits during the first day of life.

It seems to me the evidence that the second child was actually suffering from erythroblastosis is small. During pregnancy, the only evidence was an inadequate number of tests giving "rising titers." Nevertheless, the pregnancy was terminated by cesarean section at 38 weeks solely for this indication. In most centers this would be inadequate indication for abdominal delivery. Moreover, if termination of pregnancy was justified, why was cesarean section necessary? Why could not rupture of membranes followed by posterior extract of pituitary have been used prior to cesarean section?

What was the relation of placental weight to fetal weight? Certainly the liver, the first capillary filter encountered in the fetus, was said to be normal in size.

Finally, I do not think the third child necessarily died in utero (assuming that it did die) because of erythroblastosis. There are many reasons for fetal death, some of them unknown.

In other words, we cannot answer the question concerning this patient's future reproductive potential at this time because of lack of information. Is the husband truly homozygous? Was the second child seriously erythroblastotic? Did the third child die in utero because of erythroblastosis? We are not given the answers to these basic questions.

It seems to me this case presents a very common obstetric error. The doctor saw a red flag dropped on the field, namely, an Rh-negative mother. When the second red flag appeared, "rising titers" in the second pregnancy, he became frightened. Subsequent actions were predicated upon fear,

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and the necessity for intensive study of the situation was overlooked.

Abe Mickal, M.D.

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Professor and Head,

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Louisiana State University

School of Medicine

To recapitulate, we have a 26-year-old woman who is definitely hypersensitized to Rh₀ (D) antigens. She has 2 living children and does now have an intrauterine death in her third pregnancy at 34 weeks' gestation, presumably from erythroblastosis fetalis. Her husband is Rh₀-positive, homozygous. Her first baby was delivered vaginally and her second was by cesarean section, with the indication being a rising antibody titer. The problem is the mode of management of this patient with an intrauterine fetal death and Rh sensitivity.

A history of previous transfusions is not recorded on the history sheet so it is presumed that the antibody response is primarily one of pregnancy sensitization. The data lure one to believe that this patient is probably hypersensitized to Rh₀ (D) because the laboratory reports show negative results for saline (agglutins) Rho antibodies. The presence of hyperimmune or blocking antibodies is indicated by the positive albumin and Coombs tests. The trypsin test, in some patients, will indicate the presence of both saline and blocking antibodies. ABO incompatibility is possible but is not of prime importance in this case at this time.

The absence of information regarding previous blood transfusions leads one to conclude that the first pregnancy allowed the transfer of Rh₀ antigens to the maternal circulation, thereby preparing the reticuloendothelial system for the production of antibodies during the second pregnancy. It would have been interesting to have had antibody studies on this patient between the first and second pregnancy or early during the second gestation since anti-

bodies can often be detected in the late first or early second trimester.

In general, a laboratory report of Rhopositive blood implies the presence of Rho or D antigens. In this case, the father was found to be homozygous. It is assumed that this specifically refers to the Rho or D factor and this gene type can be considered as most probable, based on the present genetic knowledge of Rh-Hr factors. It is generally agreed that Rho-positive babies born from Rh-negative sensitized mothers have a more serious degree of hemolytic disease in the newborn. Since the husband is homozygous for the factor to which the mother is sensitized, it is probable that all future pregnancies will be Rho-positive and may result in early third trimester intrauterine death.

Thus far, we have considered only the laboratory findings of this couple. Now we must consider the clinical picture and the mode of management of this pregnancy, as well as make a decision relative to future childbearing activity. This could be relatively simple if, in the immediate future, there was promise of development whereby the mother's antibodies could be neutralized with a nonantigenic substance. In line with this reasoning, the work of Dr. Bettina Carter with the heptens comes to mind. Some obstetricians have used these factors with favorable results in selected cases. One also considers the negative results with vitamins and with cortisone. Unfortunately, we do not, as yet, have such aids to favorably influence the outcome in such cases.

In order to be complete, a frank discussion of this problem with both parents is mandatory. It is my policy to do this during the first pregnancy and keep both parents adequately informed thereafter, in so far as we are able in such cases. The couples are entitled to know the risk involved as well as the possible limitation of the number of healthy newborn infants they can expect in their family. In this particular case, the parents are met with a decision in regard to the desires for future pregnancy in face of recent events.

To many of us in the field of obstetrics, this may pose no particular problem. The fact that the patient has had a previous section would tend to make the decision an easy one. A repeat cesarean section at this time coupled with a sterilization procedure would insure against an unfortunate outcome of a future pregnancy. There can be little doubt that this method is final and precludes the possibility of erythroblastotic, hydropic, and/or stillborn infants.

On the other hand, this patient is 26 years of age, and her religion may permit the use of contraceptives. In the event that future developments may offer neutralizing or antiantibody substances, the patient would then have an opportunity to enlarge her family. Also, we must bear in mind that all marriages in couples of this age group are not so stable as to preclude any possibility of divorce and remarriage. This is not a pleasant thought, but the present divorce and accidental death rates cannot be completely ignored. These are some considerations that must be brought into view to arrive at a final decision. While we are considering outside matters as influence on final decision, we must take into consideration the religious aspects of the case in question; for example, Catholicism does not allow sterilization procedures.

I have discussed the genetic problems of this case with Dr. J. W. Davenport who is Director of the Department of Intravenous Therapy at Southern Baptist Hospital in New Orleans. This gentleman is "our" consultant in all problems relative to the Rh-Hr factors. He informs me that an occasional live Rh-positive baby, free of hemolytic disease, has been born to hypersensitized mothers following delivery of one or more stillborn infants.

I recently had an Rh-negative patient with the following history: Her first 2 pregnancies culminated in the births of 2 living Rh-positive children free of hemolytic disease. The third infant lived only 2 to 3 hours and postmortem examinations revealed a typical picture of erythroblastosis fetalis. Following the divorce of her first

husband, the father of the above-mentioned offspring, she remarried. Her second husband was Rh₀-positive (heterozygous). Throughout her fourth pregnancy, the antibody titers were 4-plus. However, she delivered an Rh-negative normal infant which, needless to say, has helped secure her second marriage.

There are no doubts that this case can be handled in many ways with minimal criticism for each method. I am sure I have not brought out every possible consideration and/or complication (artificial insemination, adoption, hypofibrinogenemia, etc.). To get to brass tacks as the saying goes, I would like to outline my methods for the handling of this case.

- 1. Full and frank discussion of all facts with husband and wife relative to the present situation as well as to possible future considerations.
- 2. Close observation of the patient with hematocrit level, bleeding time, coagulation time, and fibrinogen levels determined at 5 to 7 day intervals.
- 3. Observation of the patient at 5 day intervals for effacement and dilatation of the cervix. At the first sign of adequate effacement, a judicious induction of labor with Syntocinon or Pitocin under personal observation. This can be done even though the patient has had a previous cesarean section.

The length of time for observation is depedent on many factors: (a) attitude of patient toward her present situation; (b) laboratory reports—especially the fibrinogen level—as it would be to the best interest of this patient to solve this problem, if possible, without the onset of hypofibrinogenemia and its resulting complications; (c) condition of the cervix—conservative management to be the procedure of choice as long as all other factors remain within normal limits.

- 4. I would not recommend a sterilization procedure on this patient but would (in non-Catholics) give adequate instruction toward birth control.
 - 5. If, in spite of all previous discussions

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with patient and husband relative to their future childbearing functions, pointing out the possibility of remarriage, etc., and in case it became necessary to empty the uterus by hysterotomy and she and her husband definitely requested a sterilizing procedure such a procedure should be resorted to with proper consultation.

Reviews of new books

Ovum Humanum. By Landrum B. Shettles. 79 pages, 64 figures, 1 colored plate. New York, 1960, Hafner Publishing Co. \$6.00.

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The book Ovum Humanum is an attempt to give a pictorial review of the normal growth, maturation, fertilization, syngamy, and segmentation of the human ovum. All of the 64 figures and one color plate of human eggs portrayed in this book were photographed and described by the author, Dr. Landrum B. Shettles. We agree with the statement in the preface that the "paucity of direct observation on the human ovum during its growth, maturation, fertilization and in the week of its preimplantation life" has handicapped our understanding of this phase of human development. If this hiatus is to be filled and our knowledge of the preimplantation stages advanced, the evidence for such knowledge must be documented by observations that are sound and irrefutable.

The human ovum shown in the color plate (live, in natural color) has now been widely published as an excellent example of a "living human ovum." It is well known that normally there is some shrinkage of the vitellus as the time of ovulation approaches, but in the egg specimen illustrated in this book, shrinkage has exceeded by far the normal limits of living mammalian eggs. The excessive shrinkage of this egg is obvious when one compares the size relationships of the eggs shown in Figs. 33 and 50. The vitellus of the egg in question is likewise proportionately smaller than even one of the blastomeres shown in the two-celled egg in Fig. 57. That this is an example of a normal living human ovum is somewhat unlikely.

This book was no doubt to be a scientific

presentation of a series of critical observations on the growth and development of the human egg, but a pictorial presentation on any subject is only as valuable as the pictures accurately illustrate the point. Figs. 1 through 10 are photomicrographs of intraovular eggs which purport to show the growth of the oocyte and the proliferation of the granulosa cells in the development of the egg within the ovarian follicles in the human. With the exception of Figs. 1 and 2 the preparations are quite good histologically. Unfortunately, there is no indication of magnification in any of the photographs. An examination of the sequence of photographs from Figs. 4 through 10 must lead to the conclusion that the egg actually becomes smaller as the follicle grows.

The quality of the photographs taken with phase contrast objectives leaves much to be desired. For example, Fig. 13 is supposed to show a nucleolus dissected free from its nucleus. A reader unfamiliar with this material would not be able to recognize the nucleolus. Again, no size relationships or other points of reference are indicated. If Figs. 12 and 13 are compared one could only conclude that a nucleus rather than a nucleolus is portrayed.

Many of the short sentences and paragraphs used to describe the photomicrographs contain statements of presumed factual material that are unwarranted and based on insufficient evidence.

The specific role of the oviducal mucosa in the removal of the corona radiata cells is not an established fact and needs investigation. The didactic statements that polyovular follicles result in multiple pregnancies is based on the most tenuous evidence.

Ovular growth and maturation follows a defi-

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nite pattern for each species of mammals. It has been established clearly that isolation of eggs from their normal follicular environment may be a sufficient stimulus to imitate activation. It is well known also that immature eggs may be activated and/or fragment in vitro but this does not mean that they may undergo normal maturation changes, be fertilized, and undergo normal segmentation.

Eggs recovered at random from ovarian follicles of varying size would be in different stages of growth and maturation. The impression one gets from this book is that any egg recovered from an ovary may undergo maturation in vitro, be fertilized, and cleave.

In many of the photographs of "living eggs" it is impossible to delineate the structures described. Fig. 29, for example, purports to show the formation of the first polar body. The unlabeled photograph is incomprehensible even to individuals that have had wide experience with this type of material.

The sequence of photographs and descriptions of the nourishment of the intraovular egg raises grave doubts as to the accuracy and interpretation of the observations. Contrary to the author's statements, the nature by which the growing mammalian egg receives its nourishment is as yet unknown. If one reviews the recent work on the electron microscopic appearances of the egg membranes and of the attached corona cells, one is convinced that the passage of materials into the eggs of mammals is related more accurately to membrane phenomena than to the corona cells pumping their cytoplasm into the perivitelline space.

The observations on sperm penetration described by Shettles need to be confirmed. There is no evidence, on a comparative basis, that the cumulus and corona cells need to be dispersed before sperm penetration and fertilization can be effected. In fact, evidence is accumulating which indicates that the reverse is more likely to be the case. The suggestion that fertilization of a degenerating polar body may lead to hydatidiform mole and Mongolism, and certain triplet, quadruplet, and quintuplet gestations is unfounded.

From the experience of those who have examined fresh eggs of many different mammals, one is concerned over the author's lack of appreciation for the phenomenon of oocyte fragmentation. If the "segmenting eggs" shown in Figs. 57 through 64 are carefully examined, one

is astonished over the lack of even a single clearly defined nucleus in any of the segmenting blastomeres.

Fragmentation of the vitellus is a very common phenomenon in the eggs of mammals. It has been repeatedly demonstrated that unfertilized eggs may undergo segmentation into a number of fragments which closely simulate blastomeres. Some of these fragments may even contain small nuclei with nucleoli while others may be free of these elements.

The preimplantation period of human development is indeed an important one and deserves a great deal of attention but there is little in Shettle's book that gives one confidence that much enlightenment has been shed on the subject.

Obstetrics. By J. P. Greenhill. Twelfth edition. 1098 pages, 1219 illustrations. Philadelphia, 1960, W. B. Saunders Company. \$17.00.

Expansion of knowledge basic to the study of clinical subjects has been so rapid in recent years that the author of a standard textbook faces an imposing task in bringing forth a new edition. Oversized to begin with, most of these volumes can accommodate major additions of new material only by an increase in bulk or an unfortunate compression of important chapters.

In his latest effort, Greenhill has succeeded admirably in the matter of rejuvenation. Twenty-three chapters, more than a fourth of the book, have been given over to contributing authors in special fields. Many of these new sections are of outstanding quality, and the book gains in authority as a result. The fact that this has been accomplished with an increase in length of only 10 pages over the eleventh edition is testimony to the revision necessary in the remaining text.

The opening section is devoted to the physiology of reproduction and contains a lucid account of the physiology and biochemistry of the placenta by Ernest W. Page and an excellent chapter on endocrine changes in normal pregnancy by M. Edward Davis and E. Jurgen Plotz. The material on the early stages of placentation and embryological development is heavily larded with anatomical detail and terminology; it is beautifully illustrated but the text lacks the continuity needed by a student of obstetrics. There are also errors in fact (the statement that the female has two y chromosomes, which made its

appearance in the eleventh edition, is faithfully reproduced in the twelfth). An introductory chapter on genetics would be an asset in this and other obstetrical texts.

The second section deals with the physiology and conduct of labor, and discusses the details of mechanism and clinical management with clarity. There is a new chapter on the mechanism of labor in cephalic presentation by Erik Rydberg, and a very comprehensive chapter on analgesia and anesthesia. This reviewer questions the wisdom of including induction of labor by divided intramuscular dosage among the indications for use of pituitary extract, but the intravenous use of Pitocin is thoroughly covered in a subsequent chapter.

In the second portion of the book, concerned with the pathology of pregnancy, there is a fine chapter by Charles McCartney on toxemia, which is an excellent summary of knowledge of this disease. The chapters on standard obstetrical complications are conservative, and occasionally historical in tone. One wonders how many of today's students will ever see, let alone use, the Voorhees bag in management of placenta previa.

The diseases of the various systems are carefully and completely covered. The chapter on erythroblastosis is authoritative and well-illustrated. Acosta-Sison's chapter on diseases of the chorion is a valuable addition to the book, for it includes much clinical wisdom and sound judgment. Some pathologists will disagree with her belief in the syncytioma, and some clinicians will balk at the use of the uterine sound in diagnosis of hydatidiform mole, but these do not detract from the value of the chapter.

The section on the pathology of labor retains the sound, conservative principles which have characterized previous editions. A new chapter on perinatal brain injury with reference to cerebral palsy is a studious presentation of the obstetrical background of this disease. Perhaps too studious, for an obstetrical perspective is lacking and there is little appreciation of the fact that obstetrical judgment frequently involves the acceptance of lesser risks.

In the chapter on forceps delivery, Fig. 789 illustrating a low forceps delivery shows, in the portion labeled A, something perilously close to a brow-mastoid application. For the most part, the illustrations are most instructive. Near the end of the book there is a chapter on medicomoral problems by the late Herbert Schmitz, which presents in clear and unpretentious style

the views of the Roman Catholic church relative to many obstetrical problems. This will prove invaluable to students and physicians alike.

Treatment of Cancer and Allied Diseases— Tumors of the Breast, Chest and Esophagus. Edited by Geo. T. Pack and Irving M. Ariel. Second edition. Volume 4, 667 pages, 650 illustrations. New York, 1960, Paul B. Hoeber, Inc. \$30.00.

As the area most commonly affected by cancer is the thoracic region, this volume which deals with this problem is of considerable significance. The editors have collated the contributions of 67 authorities on various aspects of the problems involved.

The editors note that, with regard to breast cancer the failure of present-day methods of treatment to lower the death rate makes it imperative to evaluate critically all facfors involved. The addition of the T.N.M. method of staging the extent of disease is a worthwhile addition. The chapter on chronic mastitis is quite complete as well as clear in its exposition. The chapter on hormonal therapy of mammary cancer is extensive and a very valuable clear guide for such treatment.

The poor results obtained from the treatment of primary lung cancer and esophageal cancer are noted and documented. The value of pulmonary resection for isolated lung metastasis is also noted—15 to 16 per cent of patients subjected to such therapy have survived 3 years or longer.

One is impressed with the profusion and the excellence of the illustrations. One notes, too, the extreme paucity of reference to chemotherapy (except in lymphomas). There is no reference to the use of chemotherapy as an adjunct to surgery or radiation. This lack of consideration of this modality of therapy must be taken as an indication of its inadequacy in the eyes of the editors and the contributors.

The bibliography is an excellent one.

On the whole, this volume makes an excellent reference text for those interested in the management of cancer.

Adventure to Motherhood. By J. Allan Offen.
70 pages, illustrated. New York, 1960,
Taplinger Publishing Company. \$2.95.
Adventure to Motherhood is a picture story of
Betsy and Jim; it is a young couple's adventure

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into parenthood. A quick perusal of the book reveals the intimate step-by-step process of pregnancy and childbirth in beautiful colored photography, which is very impressive. In reading seriously, there are many surprises, especially in the styling of the book-no chapter headings, and no page identification, and the introduction of the self-diagnosed Betsy filling in her own medical history form. The text is simple, pertinent, and matter-of-fact, covering a wide range of subjects including methods of boosting morale, the use of anesthesia, episiotomy, and forceps delivery. Following the text is a summary of "do's and dont's" during pregnancy and a useful page for filling in essential information which will be needed during an Adventure to Mother-

This book is recommended for young married couples when they wish to do some leisurely, pictorial reading.

Electrohysterography. By Saul David Larks. 123 pages, 44 figures, 2 tables. Springfield, Illinois, 1960, Charles C Thomas, Publisher. \$5.75.

Just as the pioneers in electrocardiography and electroencephalography were met with resistance to the acceptance of their novel approaches, the author of this monograph suggests the same disappointing initial experience for workers in this new field of electrohysterography.

The subject is introduced through a brief historical review of bioelectric phenomena, and an anatomical and physiological description of the development and function of the uterus is given. This introductory material is probably of more value to the biophysicist than to the physician.

The methods of measuring the potentials of the uterine muscle are very simple because the electronics field offers excellent amplifiers and recorders ideally suited to this type of electrical dynamics. Because of this technical ease, the investigator can attend to the intricacies of the experiment instead of to the problems of electronics.

This monograph has a single technical thesis: that the initiation and propagation of the electrical concomitant of uterine contraction is analogous to the electrical activity of the heart. The author makes a convincing case for this analog, the theoretical data fitting well the observed potential patterns.

Electrohysterograms taken in labor, both normal and abnormal, present a series of interesting dynamical pictures, but lack statistical significance. Statistical depth and a larger number of leads are presumably left for future work. The reviewer agrees with the author that electrohysterography is an infant field and that its pursuit will surely be rewarding. Its development will be accelerated and facilitated by the ready availability of tools of measurement and analysis.

Surgical Errors and Safeguards. By M. Thorek and 23 contributors. Fifth edition. 652 pages, 455 figures. Philadelphia, 1960, J. B. Lippincott Company. \$25.00.

The fifth edition of this well-established book comes out as a multi-author book, with 22 collaborators, a number of them distinguished. The authors' own sections retain their intensely personal conversational style.

Essentially, this is a brief textbook of surgery, written in didactic fashion. It covers the specialties, as well as general surgery, and there is a completely new section devoted to cardiovascular surgery. That material is effectively presented in almost atlas form, which is remarkably clear.

Books received for review

- Annales Universitatis Mariae Curie-Sklodowska, Volume XIV. 354 pages, Lublin Nakladem Uniwersytetu Marii Curie-Sklodowskiej, I Akademii Medycznej W. Lublinie, 1960.
- Atlas der Gynakologischen Anatomie. By Heinrich Martius and Kathe Droysen. 118 pages, 134 figures. Stuttgart, 1960, Georg Thieme Verlag. \$11.65.
- Blood Diseases of Infancy and Childhood. By Carl H. Smith. 572 pages, 51 figures, 21 tables. St. Louis, 1960, The C. V. Mosby Company. \$17.00.
- Cardiac Disease in Pregnancy. By Curtis Lester Mendelson. 385 pages, 141 illustrations. 68 tables. Philadelphia, 1960, F. A. Davis Company. \$13.50.

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Colloques—La physiopathologie circulatoire foetale humaine en dehors du travail de la parturition. 218 pages. Tenus a la Clinique Gynecologique et Obstetricale de l'Universite de Gand, 1959.

Congenital Malformations. By G. E. W. Wolstenholme and Cecilia M. O'Connor. 308 pages, 91 illustrations. Boston, 1960, Little, Brown & Co. \$9.00.

Human Pituitary Hormones, Ciba Foundation Colloquia on Endocrinology. By G. E. W. Wolstenholme and Cecilia M. O'Connor. Volume XIII, 336 pages, 86 illustrations. Boston, 1960, Little, Brown & Co. \$9.50.

L'Annee éndocrinologique. 210 pages, 12 figures. Paris, 1960, Masson & Cie.

Lectures on Haematology. By F. G. J. Hayhoe. 347 pages. New York, 1960, Cambridge University Press. \$11.50.

Les fonctions de nidation uterine et leurs troubles. 392 pages, 82 figures, 40 tables. Paris, 1960, Masson & Cie.

Les troubles fonctionnels uretro-vesicaux en gynecologie. 294 pages, 59 figures, 7 tables. Paris, 1960, Masson & Cie.

Medical and Biological Research in Israel. By Moshe Prywes. 562 pages. New York, 1960, Grune & Stratton, Inc. \$8.00.

Obstetrical and Gynaecological Pathology. By R. E. Rewell. 435 pages, 19 tables. London, 1960, E. & S. Livingstone, Ltd. \$10.00.

Over de Behandeling. By R. J. J. Omers. 128 pages. Heerlen, 1960, N. V. Uitgeverij Winants.

Resuscitation of the Newborn Infant. By Harold Abramson. 274 pages, 35 figures, 17 tables. St. Louis, 1960, The C. V. Mosby Company. \$10.00.

Surgical Treatment of Trauma. By Preston A. Wade. 779 pages. New York, 1960, Grune & Stratton, Inc. \$26.50.

Survey of Research in Gestation and the Developmental Sciences. By Jack Davies. 203 pages, 11 tables. Baltimore, 1960, Williams & Wilkins Company. \$6.00.

A System of Medical Hypnosis. By Ainslie Meares. 484 pages, 57 illustrations. Philadelphia, 1960, W. B. Saunders Company. \$10.00.

A Text Book of Gynaecology. By K. M. Masani. Third edition. 706 pages, 148 figures. Bombay, 1960, Popular Book Depot. Rs. 28.00.

Selected abstracts

Acta geneticae medicae et gemellologiae Vol. 9, No. 3, 1960.

*Gedda, L., and Poggi, D.: The Importance of Placentation on the Birth Weight of Twins, p. 271.

Gedda and Poggi: Importance of Placentation on Birth Weight of Twins, p. 271.

The authors have analyzed the birth weight differences of twins as to placentation, zygosity, and sex. They have statistically analyzed the weight differences in 124 monozygotic and 124 dizygotic twin pairs. Zygosity and placentation but not sex are shown to play a distinct role. The greatest differences in weight are in dizygotic twins with a single placenta. There is more circulatory imbalance in single placentas and more intrapair weight difference which may explain the higher incidence of blighted fetuses in monozygotic twin pregnancies or the high inci-

dence of discordant congenital heart disease in female monozygotic twin pregnancies.

Louis A. Gentile

American Journal of Pathology

Vol. 37, August, 1960.

Gunn, Samuel A., Gould, Thelma Clark, and Anderson, W. A. D.: Effect of X-Irradiation on the Morphology and Function of Rat Testis, p. 203.

Anesthesiology

Vol. 21, July-August, 1960.

James, L. Stanley: Effect of Pain Relief for Labor and Delivery on the Fetus and Newborn, p. 405.

British Medical Journal

Vol. 2, Aug. 27, 1960.

Giles, C., and Burton, Harold: Observations on Prevention and Diagnosis of Anaemia in Pregnancy, p. 636.

^{*}These articles have been abstracted.

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Cancer Research

Vol. 20, August, 1960.

- Johnson, I. S., Wright, H. F., Svoboda, G. H., and Vlantis, J.: Antitumor Principles Derived From Vinca Rosea Linn. I. Vincaleukoblastine and Leurosine, p. 1016.
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Vol. 174, Sept. 3, 1960.

Walters, Waltman, Ramsdell, J. A., and Johnson, C. E.: Thirty-Four Pregnancies After Repair of Bile Duct, p. 26.

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Vol. 39, September, 1960.

- Bonting, S. L., Pollak, V. E., Muehrcke, R. C., and Kark, R. M.: Quantitative Histochemistry of the Nephron. II. Alkaline Phosphatase Activity in Man and Other Species, p. 1372.
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- Pollak, V. E., Bonting, S. L., Muehrcke, R. C., and Kark, R. M.: Quantitative Histochemistry of the Nephron. IV. Alkaline Phosphatase and Lactic Dehydrogenase Activities in Renal Tubular Diseases, p. 1386.
- Pollak, V. E., Bonting, S. L., Muehrcke, R. C., and Kark, R. M.: Quantitative Histochemistry of the Nephron. V. Alkaline Phosphatase and Lactic Dehydrogenase Activities in Lupus Nephritis, p. 1304

Journal of Obstetrics and Gynaecology of India

Vol. 10, June, 1960.

- Dhall, S. R., and Taneja, O. P.: Study of Erythrocyte Sedimentation Rate Changes in Obstetrics and Gynecology, p. 435.
- Upadhyay, S. N., and Achari, K.: Mechanism and Management of Inversion of Uterus, p. 447.
- Parikh, Mahendra N.: Face Presentation, p. 456.

The Irish Journal of Medical Science

Vol. 1, June, 1960.

*Breathrach, C. S.: The Cellular Distribution of Fetal and Adult Hemoglobin, p. 286.

Breathrach: Cellular Distribution of Fetal and Adult Hemoglobin, p. 286.

The technique of Kleihauer, Braun, and Betke was used to study the distribution of the two types of respiratory pigments within the erythrocyte in early infancy. An analysis of the results appear to indicate that fetal cells which contain the retained and eosin stained fetal hemoglobin are filled with this variety exclusively and that the eluted cells contained adult hemoglobin alone. More important than the fact that fetal hemoglobin and fetal cells disappear from the blood at the same age is the demonstration that the rate of disappearance the slopes of the curves) are practically the same. At 8 weeks when anisocytosis is no longer a feature about 50 per cent of the hemoglobin and of the red cells is of the fetal variety. The regression lines constructed from observed values are so consistently close to one another that the possibility of mixtures of hemoglobin within the cells is precluded. It is concluded that fetal corpuscles contain fetal hemoglobin and adult cells adult hemoglobin, exclusively.

Edward Solomons

The Lancet

Vol. 2, Sept. 10, 1960.

Baird, Sir Dugald: The Evolution of Modern Obstetrics, p. 557.

New York State Journal of Medicine

Oct. 1, 1960.

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Vol. 185, August, 1960.

Bishop, P. M. F.: Oral Contraceptives, p. 158.

September, 1960.

Howkins, John: Endometriosis, p. 265.

Davidson, Samuel: Prolapse and Its Management, p. 271.

Russell, C. S.: Malformations of the Female Genital Tract, p. 285.

Rhodes, Philip: Tuberculosis of the Genital Tract in Women, p. 290.

Hamilton, John: Problem of Vaginitis, p. 29%.

Winterton, W. R.: Etiology and Treatment of Amenorrhoea, p. 301.

de Vere, R. D.: Problem of Dysmenorrhoea, p. 308.

Proceedings of the Staff Meetings of The Mayo Clinic

Vol. 35, Aug. 31, 1960.

Decker, David G.: Invasive Carcinoma of the Uterine Cervix: General Considerations, p. 505.

Soule, Edward H., and Dahlin, David C.: Cytodetection of Preclinical Carcinoma of the Cervix: 12 Years' Experience With Initial Screening and Repeat Cervical Smears, p. 508.

Mussey, Elizabeth: Carcinoma in Situ of the Uterine Cervix, p. 513.

Van Herik, Martin: Radiation Therapy for Carcinoma of the Cervix, p. 518.

Pratt, Joseph Hyde: Surgical Treatment of Carcinoma of the Uterine Cervix, p. 523.

Proceedings of the Society for Experimental Biology and Medicine

Vol. 104, 1960.

*Lough, S. A., Hamada, G. H., and Comar, C. L.: Secretion of Strontium 90 and Calcium in Human Milk, p. 194.

*Coffin, G. S., Hook, W. A., and Muschel, L. H.: Antibacterial Substances in Placentas and Serums of Mothers and Newborn Infants, p. 239.

Lough, Hamada, and Comar: Secretion of Strontium 90 and Calcium in Human Milk, p. 194.

The authors have attempted to study the relationship of strontium 90 and calcium of the diet, the body, and human milk. Calcium and strontium of milk are derived largely from diet and from skeletal stores. Levels of Sr⁹⁰ and calcium in the diet and secreted milk were measured in 5 normal postpartum women. The authors' results suggest that the Sr⁹⁰/Ca ratio in mother's milk is one tenth of that in her diet. By extrapolating figures obtained in controlled animal experiments, it would appear that the Sr90/Ca ratio in blood and bone is 0.25 that in the consumed diet. The figures presented are of interest in estimating radiostrontium levels of infants from their diet and from the diet of the mothers in those who are breastfed.

Edward E. Wallach

Coffin, Hook, and Muschel: Antibacterial Substances in Placentas and Serums of Mothers and Newborn Infants, p. 239.

Antibacterial activity of maternal serum, umbilical cord serum, and placental preparations obtained immediately following delivery was tested against 7 species of bacteria. Both sera and placental preparations demonstrated bactericidal activity against the same organisms. Levels of properdin, complement, and lysozyme were measured in each specimen. In all cases lysozyme levels were higher in the serum of newborn babies than in maternal serum. Placental preparations contained lower properdin and complement levels than the sera. It is concluded that placental bactericidal activity is derived from the maternal blood, with little or no independent activity. Passive transfer of properdin and complement is thought to occur from mother to fetus across the placenta. Lysozyme may be selectively transmitted or produced by the fetus or its membranes. Protection of the fetus from bacterial infection occurs in the placenta by two mechanisms: (1) mechanical impedance and (2) transmission of substances from mother to fetus.

Edward E. Wallach

Public Health Reports

Vol. 75, 1960.

*Moriyama, Iwao M.: Recent Changes in Infant Mortality Trends, p. 391.

Moriyama: Recent Changes in Infant Mortality Trends, p. 391.

The rate of decrease of infant mortality in the United States, which began in 1933 at 4.3 per cent per annum, has been 2.0 per cent per annum since 1950. The decline in rate of decrease has been more marked in non-white population.

Subdivision by age reveals that the rate has remained unchanged since 1933 for infants from 1 to 6 days old. The decline has occurred in the group 1 to 11 months of age. There are now 8 neonatal deaths (under one month of age) for every 3 postneonatal deaths (one to 11 months of age). Neonatal deaths are related to prematurity, birth injuries and asphyxia in 75 per cent of the cases; 15 per cent are related to malformations, and only 9 per cent to infectious disease. Postneonatal deaths are predominantly related to infectious disease, namely, influenza, pneumonia, and enteritis.

In 1933 infectious disease mortality began to

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drop, causing a decline in the rate of infant mortality. This was further demonstrated with the introduction of penicillin in 1945-1946, causing the rates to decline sharply. However, almost immediately the trend for non-white infants began to level, and since 1950, the trend for white infants had begun to level. The reason for this difference in response to treatment of infectious disease is not well elucidated.

It may be noted then that since prematurity, birth injuries, asphyxia, and malformations cause the bulk of the neonatal deaths, which in turn are responsible for the bulk of all infant deaths, there will be a basic flat trend in mortality curves until these entities are better handled. Small changes in infectious disease mortality will be perceived as large changes in postneonatal trends and as significant changes in total infant mortality trends. Therefore, immediate improvements must come from better treatment of influenza, pneumonia, and enteritis.

Carl J. Pauerstein

Southern Medical Journal

Vol. 53, September, 1960.

*Binder, S. S., and Mitchell, B. A.: The Control of Intractable Pelvic Hemorrhage by Ligation of the Hypogastric Artery, p. 837.

Binder and Mitchell: Control of Intractable Pelvic Hemorrhage by Ligation of the Hypogastric Artery, p. 837.

The role of ligation of the hypogastric artery in the management of uncontrollable pelvic hemorrhage is discussed. Ligation of the hypogastric artery may be preceded by attempted ligation of individual bleeding points, packing, and the use of hemostatic agents with or without administration of blood. Indications for this procedure include intractable hemorrhage from cervical or endometrial carcinoma, uncontrolled bleeding at the time of pelvic operation, and postoperative and postpartum hemorrhage. Studies have shown the collateral circulation of the branches of the hypogastric artery to be adequate. These collaterals include: (1) the uterine anastomoses with the ovarian artery; (2) the middle hemorrhoidal

anastamoses with the superior hemorrhoidal (from the inferior mesenteric) and the inferior hemorrhoidal (from the internal pudendal branch of the hypogastric); (3) anastamoses between the branches of the obturator and the inferior epigastric (from the external iliac artery); (4) the inferior gluteal anastamoses with the circumflex and perforating branches of the deep femoral artery; (5) the superior gluteal and (6) the iliolumbar anastamoses with the lumbar arteries of the aorta; and (7) the vesicoarterial anastamoses with the uterine and vaginal branches of the hypogastric artery.

The technique involves opening the posterior parietal peritoneum over the promontory of the sacrum and dissecting laterally until the bifurcation of the common iliac is identified. After dissection of the hypogastric artery from the underlying internal iliac vein, the hypogastric is ligated, preferably distal to the ureteral branch, using silk, cotton, or chromic catgut. Ischemic necrosis of the bladder, rectum, vagina, or buttocks from impaired blood supply is considered unlikely. Four case reports are presented in which this measure was employed with success. Edward E. Wallach

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Vol. 53, October, 1960.

Voltz, P. W., Jr., Mallams, J. T., and Swindell, G. E.: Radium Attenuation in the Treatment of Carcinoma of the Cervix, p. 1205.

Toniette, S. J., Velarde, A. and Williams, G. A.:
Primary Carcinoma of the Fallopian
Tube, p. 1253.

Surgery, Obstetrics and Gynecology

Vol. 17, April-June, 1960.

Dao, Thomas L.: Adrenalectomy for Mammary Cancer: A Review, p. 75.

Western Journal of Surgery, Obstetrics and Gynecology

Vol. 68, July-August, 1960.

Stein, Arthur A.: Carcinoma in Situ of Cervix Uteri, a Histologic Histochemical Study, p. 6. Preg To T Gilb Gest 625

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Correspondence

Pregnancy complicated by pyocolpos

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ervix nical The report of Drs. William Kirkley, J. C. Gilbert, Jr., and G. C. McDaniel, "Six Months' Gestation Complicated by Pyocolpos" on page 625 of the October, 1960, issue of the JOURNAL, reminds us of a Bedouin custom long practiced out here. In the Arabian desert following delivery complicated by laceration of the perineum or postpartum hemorrhage, the vagina is often packed with salt. When these women are seen in subsequent pregnancies the lumen of the vagina may scarcely admit one finger.

After many hours or even days of futile labor these poor women are brought to the hospital. Before the development of modern hospitals in Saudi Arabia they were often brought to the American University Hospital, arriving after days of donkey or camel travel. They were seen with a macerated fetus and sometimes a ruptured uterus. In one case a macerated fetus was sloughed through an abscess in the left inguinal region some 14 days after the onset of labor.

Fortunately, such neglected cases are now rare; however, the practice of "salt" cauterization persists with consequent soft tissue dystocia requiring cesarean section for delivery.

William Bickers, M.D., Chairman

Department of Obstetrics and Gynecology American University Hospital Beirut, Lebanon Nov. 30, 1960

Items

Foundation Prize of the American Association of Obstetricians and Gynecologists

Manuscripts of not more than 5,000 words, in three copies, under a nom de plume—the real name of the author in a separate, sealed envelope—must be in the hands of Dr. Jean Paul Pratt, Henry Ford Hospital, Detroit, Michigan, before April 1, 1961.

Those eligible for this \$500 prize include (a) interns, residents, or graduate students in obstetrics and gynecology, and (b) persons with an M.D. degree, or a scientific degree approved by the Prize Award Committee, who are actively practicing, teaching, or engaged in research in obstetrics and gynecology.

American Board of Obstetrics and Gynecology

The next scheduled examinations (Part II), oral and clinical, for all candidates will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board Ápril 8 through 15, 1961. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participated in the Part I Examinations will be notified of their eligibility for the Part II Examinations as soon as possible.

The deadline date for the receipt of new and reopened applications for the 1962 examinations is Aug. 1, 1961. Candidates are urged to submit their applications as soon as possible before that time.

Robert L. Faulkner, M.D. 2105 Adelbert Road Cleveland 6, Ohio



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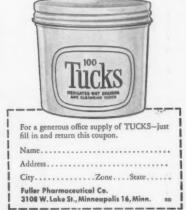
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but certainly not as a toilet wipe when anal areas are sensitive. Unlike harsh, dry wood pulp toilet papers, Tucks are soft cotton flannel pads mildly medicated with witch hazel (50%) and glycerin (10%). Tucks are ideal for routine toilet care when treating pruritus ani et vulvae, diaper rash, hemorrhoids, following episiotomy or hemorrhoidectomy, and in other anorectal conditions. Tucks cleansing, mildly astringent action hastens healing and helps assure patient comfort. Tucks are available at busy prescription pharmacies everywhere in jars of 40 and 100.





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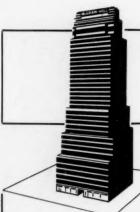
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By Frank F. Tallman, M.D. 426 pp., 53/8 x 8, \$11.00

Dr. Tallman's work stresses those therapeutic methods used in the treatment of emotional problems in office practice that can be understood and applied by physicians who are not specialists in psychiatry. This book integrates material on reactions to stress, behavior patterns, interpersonal relationships and emotions with the laboratory and machine aspects of clinical medicine. Current literature, relating to the clinical aspects of psychosomatic medicine, appears after chapters to supplement the material in the text.

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American Medical Association STANDARD NOMENCLATURE OF DISEASES AND OPERATIONS, 5th Edition

Edward T. Thompson, M.D., F.A.C.H.A., Editor; Adaline C. Hayden, C.R.L., Associate Editor. Approx. 1,000 pp., 55/8 x 83/8, In press

This new fifth edition brings the Standard Nomenclature in line with the changing concepts of medicine, particularly changes in etiology. New clinical conditions as determined by research and clinical studies have been added as well as corrections in terminology and code numbers.

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1. Haden, R.L., et al.: Ann. N.Y. Acad. Sc. 49:641 (May 11) 1948.

2. Cheraskin, E.: J. Am. Dent. Assn. 58:17 (April) 1959.

*U.S. Pat. Nos. 2581850; 2506294

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condition	no. of cases	excellent/ good	fair	no response
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1. Teitel, L. H., et al.: Indust. Med. 29:150, 1960. 2. Clinical reports to the Medical Dept., Armour Pharmaceutical Company, 1959. 3. Reich, W. J., and Nechtow, M. J.: Scientific Exhibit, Amer. Med. Assoc. Conv., Miami,

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AGAINST CATHETERS & ENEMAS

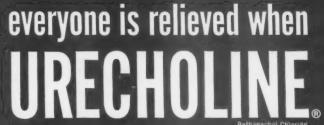
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1. Crawford, O. B.: Anesthesiology 14:278, 1953. 2. Wiedling, S.: Xylocaine, The Pharmacological Basis For its Clinical Use, Stockholm, Almquist and Wiknell, 1959.



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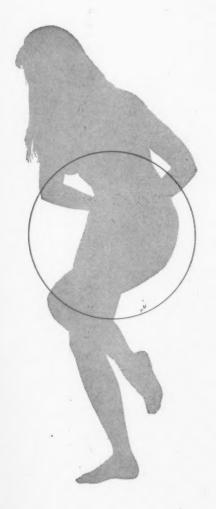


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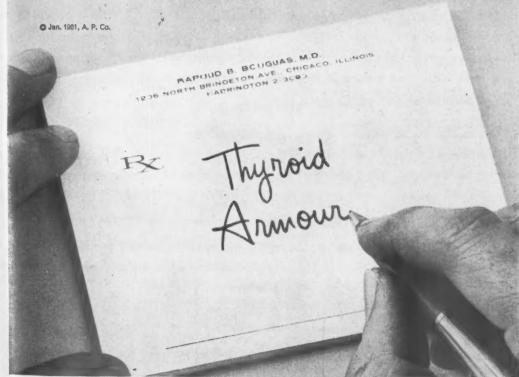
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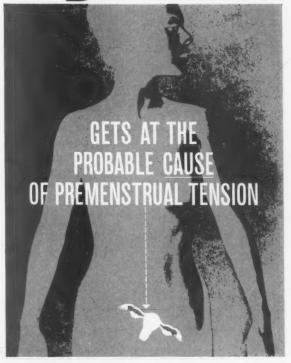
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References: 1. N. Mulla and J. J. McDonough, Ann. New York Acad. Sc., 82: (Art. 1), 182, 1959. 2. L. E. Savel, sion of Hoffmann-LaRoche inc. D. B. Gershenfeld, J. Finkel and P. Drucker, Ibid., p. 186.

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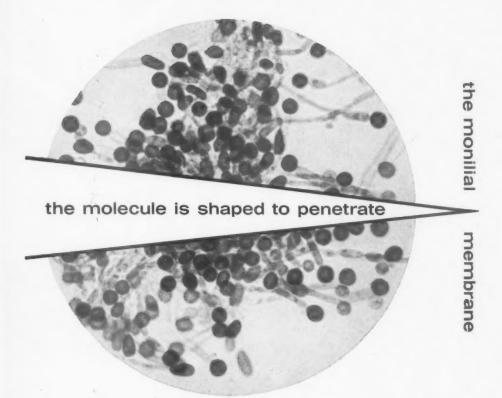
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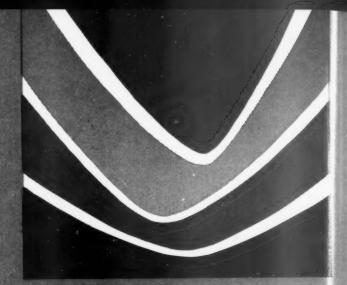
Lapan, B.: Am. J. Obst. & Gynec. 78:1320, 1959.



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TIGAN BIBLIOGRAPHY: 1. M. W. Goldberg, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 2. O. C. Brandman, ibid. 3. J. A. Lucinian and R. H. Bohn, ibid. 4. D. W. Molander, ibid. 5. B. I. Shnider and G. L. Gold, ibid. 6. W. S. Derrick, ibid. 7. B. Wolfson and F. F. Foldes, ibid. 8. L. McLaughlin, ibid. 9. W. K. Gauthier, Discussant, ibid. 10. H. E. Davis, Discussant, ibid. 11. I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, J. Newark Beth Israel Hosp., 9:189, 1958. 12. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, J. Pharmacol. & Exper. Therap., 126:270, 1959. 13. W. B. Abrams, I. Roseff, J. Kaufman, L. M. Goldman and A. Bernstein, New York J. Med., 59:4217, 1959. 14. O. W. Doyle, Clin. Med., 7:43, 1960. 15. L. A. Nathan, Curr. Therap. Res., 2:6, 1960. 16. Council on Drugs, New and Nonofficial Drugs, J.A.M.A., 172:1038, 1960. 17. O. L. Davidson, J. Tennessee M.A., 53:140, 1960. 18. O. Brandman, Gastroenterology, 38:777, 1960. 19. B. A. Robin, Maryland M. J., in press. 20. A. L. Kolodny, Am. J. M. Sc., 239:682, 1960. 21. F. Cacace, Colorado GP, 2:5, 1960. 22. J. W. Bellville, I. D. J. Bross and W. S. Howland, Clin. Pharmacol. & Therap., TIGAN® Hydrochloride-4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl) benzylamine hydrochloride



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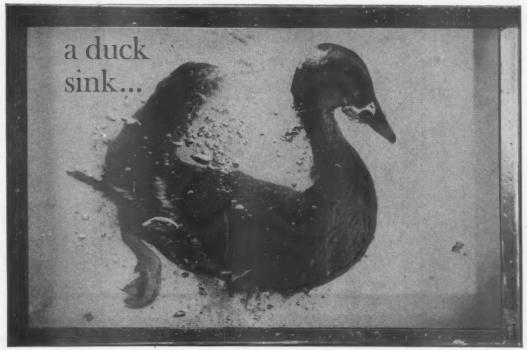
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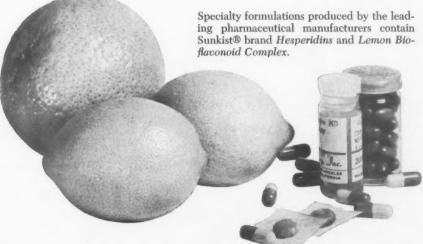
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1. N.N.R., 1959, 515; 2. Ibid., 376

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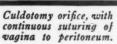
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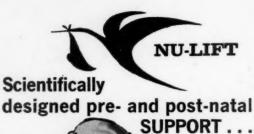
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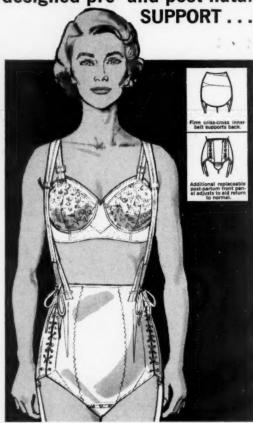
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1. Rosenfield, H. H., et al.: Obst. & Gynec. 11:222, 1958. 2. Bookmiller, M. M., and Bowen, G. L.: Textbook of Obstetrics and Obstetric Nursing, ed. 3, Philadelphia, Saunders, 1958, p. 314. 3. Hellman, L. D.: Gastroenterology.

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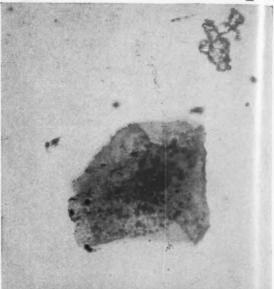
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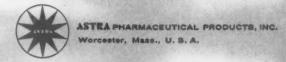
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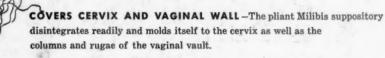
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